The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol in detecting lobular carcinoma.

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Declaration

This research study would not have been possible without the support of my family. My heartfelt gratitude goes out to my boyfriend for his understanding, encouragement and for always believing in me. Also, many thanks to my friends who have always supported me even when times got tough

Abstract

Purpose: This study evaluated and compared the diagnostic accuracy of an abbreviated protocol against a full protocol for breast MRI in detecting lobular carcinoma

Objectives: To compare the diagnostic accuracy and cancer yield of an abbreviated protocol to a full protocol using breast imaging reporting and data system classification (BI-RADS); determine diagnostic accuracy through ROC curves; calculate performance indicators for both protocols.

Methodology: 35 cases undertaken during the period January 2019 and December 2021; 20- biopsy confirmed lobular carcinoma; 15- normal (negative follow up imaging). Two radiologists independently reviewed the abbreviated protocol. The data collected was compared with data collected from initial radiological MRI reports based on the full protocol. Lesions with BI-RADS category 1 or 2 were considered negative while BI-RADS of 3,4 or 5 considered positive. Results were analysed using ROC analysis.

Results: The area under the curve obtained from each ROC curve was 1- full protocol, 0.920 and 0.922 for radiologist A and B for the abbreviated protocol respectively. The p-value (<0.05) for all the corresponding protocols indicated that each protocol diagnosed the disease state (cancer yes/no) at a statistically significant level. When using the abbreviated protocol, the diagnostic accuracy was maintained. All cancers were detected by the two radiologists with the abbreviated protocol (100% sensitivity), which was the equal to the full protocol. The specificity of the abbreviated protocol was significantly ($p<0.05$) lower for radiologists A (73.3%) and B (53.5%) when compared to the full protocol (100% for both).

Conclusions: This study was the first of its kind performed locally creating a baseline for further investigations and adding to the body of knowledge. Despite limitations, it demonstrated that the abbreviated protocol had equal diagnostic accuracy to the full protocol in the detection of lobular carcinoma.

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List of Acronyms

AAFP American Academy of Family Physicians

ABUS Automated Whole-Breast Ultrasound

ACOG The American College of Obstetrician and Gynaecologists

ACP American College of Physicians

ACR American College of Radiology

ACRIN American College of Radiology Imaging Network

ACS American Cancer Society

ADH Atypical Ductal Hyperplasia

ALH Atypical Lobular Hyperplasia

ASBrS American Society of Breast Surgeons

AUC Area Under the Curve

BI-RADS Breast Imaging Reporting and Data System

BPE Background Parenchymal Enhancement

BRCA Breast Cancer Gene

CDR Cancer Detection Rate

CEDM Contrast- Enhanced Digital Mammography

CEO Chief Executive Officer

DBT Digital Breast Tomosynthesis

DCE Dynamic Contrast Enhanced

DCIS Ductal Carcinoma in situ

DWI Diffusion Weighted Imaging

EBC European Breast Cancer

EBG European Breast Guidelines

ECIBC European Commission Initiative on Breast Cancer

ESMO European Society for Medical Oncology

EUSOBI European Society of Breast Imaging

FREC Faculty Research Ethics Committee

GDPR General Data Protection Regulation

HRT Hormone Replacement Therapy

ICC Intraclass correlation coefficient

IDC Invasive Ductal Carcinoma

ILC Invasive Lobular Carcinoma

LCIS Lobular Carcinoma in situ

MIP Maximum Intensity Projection

MRI Magnetic Resonance Imaging

NCBC National Consortium of Breast Centres

NCCN National Comprehensive Cancer Network

NPV Negative Predictive Value

PACS Picture Archiving and Communication System

PPV Positive Predictive Value

RIS Radiological Information System

ROC Receiver Operating Characteristics

SBI Society of Breast Imaging

SPSS Statistical l Package for Social Sciences software

STIR Short Tau Inversion Recovery

T Tesla

UREC University Research Ethics Committee

US Ultrasound

USPSTF United States Preventive Services Taskforce

WHO World Health Organisation

Chapter 1

Introduction

1.1 Introduction

Cancer of the breast is the most common cancer among women around the world, with a continual increase in burden over the past decade (Arnold et al., 2022). According to the Maltese National Cancer Registry (2019) there have been more than 200 new cases of breast cancer in women registered every year between the years 2007- 2019, with 378 cases registered in 2019. In 2009, Malta had the highest death rate of 34.4 per 100,000 inhabitants in Europe from breast cancer (Eurostat, 2018). Coincidentally Malta was one of the last European country to introduce a breast screening program, the same year these statistics were collected (Maltese National Cancer Registry, 2019). However, in the latest Eurostat statistics, the rate has decreased significantly, and Malta registered a mortality rate of 27.5 per 100,000 inhabitants in the year 2018 (Eurostat, 2020).

The definition of health screening varies according to culture, setting and time periods (Løberg et al., 2015). As discussed by Løberg et al (2015) all definitions include "*an identification of disease or disease precursor among presumptively healthy individuals*" (p.1). The aim behind health screening is to facilitate prevention and early detection which ultimately leads to a better prognosis (Bretthauer & Kalager, 2013). Mammography is the current gold standard screening tool for breast cancer and has been for more than five decades . Breast screening is linked to a reduction of 16-40% in the mortality rate and is one of the most cost-effective methods of breast screening (Chhor & Mercado, 2017; Koning, 2003; Feig, 2010; Tabar et al., 2003). However, mammography screening alone is not sufficient for certain groups of women, such as women with a higher than average risk of developing breast cancer (Cadiz et al., 2013; Chhor & Mercado, 2017). Women with higher risk factors for developing breast cancer need earlier and more intense health screening programs due to the risk of developing breast cancer at a younger age (Lee, Monticciolo & Moy, 2020).

Locally, women aged between 50 to 69 years are offered mammography screening every two years irrespective of their risk, however, evaluations are still being made to introduce programmes specifically for high-risk women (Ministry of Health, 2017). There has been a growing interest in MRI and evidence indicates that MRI is the most sensitive imaging modality in young high-risk women (Salem et al., 2013; Gao et al., 2021). This research study investigated the use of magnetic resonance imaging (MRI) as a screening tool for high-risk women.

1.2 Background to the study

Approximately one in eight women in the general population have a lifetime risk (>20%) for developing breast cancer (Sun et al., 2017). For some, the risk of breast cancer is increased, and these individuals are considered as high-risk women. Breast cancer screening for high-risk women starts at a very young age due to the high probability of early onset of breast cancer, as more than 50% of women with high genetic risk are affected with breast cancer before the age of 50 years (Podo et al., 2002).Women who have genetic mutations (Breast Cancer Gene (BRCA) 1 or 2), history of breast cancer, family history of breast cancer or prior chest radiation are all at an increased risk of breast cancer (Monticciolo et al., 2018). Such women may require mammographic surveillance to start from a younger age, when the breast is usually much denser thus mammography would also be less sensitive to detect diseases (Trecate et al., 2006). Younger women are more likely to have almost all of their breast consisting of dense tissue in comparison to the breast of older women having more fatty tissue, since with age there is regression in the breast parenchyma (Liao et al., 2020). Breast density is not a fixed personal characteristic however it is a dynamic process which changes over a woman's lifetime (Pinsky & Helvie, 2010). The frequency of heterogeneously or extremely dense breast tissue decreased with age with 85.3%, 81.6%, 77%, 42.9% and 22.1% in the age groups 25-29, 30-34, 45-49, 55-59 and 65-69 respectively

(Ji et al., 2021). Dense tissue attenuates x-ray more than fat thus, dense tissue appears opaque (white), while fatty tissue appears radiolucent (dark) on a mammogram (Chen et al., 2015).

Women with dense breasts have a four to six fold increased risk of developing breast cancer and a low chance of detecting it with mammography (Yaghjyan et al., 2011). Since the mammographic image suffers from tissue overlapping (superimposition) and there is a higher possibility that cancer is masked by overlying dense breast tissue rather than fatty tissue (Chen et al., 2015; Pinsky & Helvie, 2010). Surveillance of high-risk patients should continue throughout their whole life and therefore would result in an accumulation of biological damage from ionising radiation administered as part of the routine mammography screening examination (Trecate et al., 2006).

MRI is a non-invasive imaging technique which does not use ionising radiation (Ghadimi & Sapra, 2019) and is not influenced by dense breasts. MRI may address the limitations presented with mammography as there is cross-sectional imaging of the breast with possible three dimensional imaging and therefore this overcomes the limitation of tissue overlapping (Lehman, 2006). MRI has the potential to measure more density-related biological properties than mammography, for example the water-fat content which is seen with Dixon imaging (fat suppression technique) (Chen et al., 2015). As stated by Podo et al (2002) MRI of the breast has become the most sensitive imaging modality for breast cancer diagnosis.

Aristokli et al. (2022) reported a much higher sensitivity to identify breast lesions with MRI when compared to mammography with a sensitivity of 94.6% and 54.5% respectively. The study by Roganovic et al. (2015) also reported a similar sensitivity in the detection of breast cancer with the use of MRI (90%). The sensitivity of MRI as an adjunct to mammography increased greatly the sensitivity over using mammography alone

(Aristokli et al., 2022; Saadatmand et al., 2019).The sensitivity of MRI and mammography combined was 98% while using mammography and MRI alone was 55% and 89% (Saadatmand et al., 2019). The sensitivity of MRI indicates its great potential in detecting cancers at an early stage when compared to mammography. The specificity of MRI, however has been greatly challenged and is significantly lower than that of mammography in studies (Saadatmand et al., 2019). The main reason for the low specificity is due to the challenge to discriminate between benign and malignant lesions (Menezes, 2014). In an MRI scan of the breast both benign and malignant lesions enhance following contrast injection with little differentiation in their characteristics (Shahid et al., 2016). A mammogram can detect calcifications unlike MRI which can help distinguish between benign and malignant lesions (Nalawade, 2009). Micro-calcifications can be the only presenting sign of breast cancer and their presentation indicates if they are benign or malignant requiring careful evaluation (Nalawade, 2009).

The contraindications associated with MRI include women who have pacemakers, artificial heart valves and cochlear implants (Ghadimi & Sapra, 2019). Such women may not be scanned using MRI or may need to be scanned only under certain conditions, while claustrophobic patients may not complete the exam (Ghadimi & Sapra, 2019). Despite the high diagnostic performance of breast MRI, the length of the examinations usually ranges from 30 to 40 minutes and the cost of each MRI examination hinders its routine application as a screening modality (Oldrini et al., 2018). To increase the availability of screening with MRI, Kuhl et al. (2014) was the first to introduce the use of an abbreviated protocol to counteract such limitations to reduce the time and cost of each examination which provided very promising results.

Kuhl et al (2014) reported on the feasibility of an abbreviated protocol which consisted of an unenhanced T1 weighted and first contrast enhanced T1 weighted sequence,

Maximum Intensity Projection (MIP) imaging and subtraction imaging. The abbreviated protocol was generated from the full diagnostic protocol (Kuhl et al., 2014). The authors concluded that there was a significant reduction in image acquisition and interpretation time without compromising the diagnostic accuracy (Kuhl et al., 2014). Following Kuhl et al. (2014) further studies followed on the same principle and different abbreviated protocols with various sequences were considered to determine which protocol provides the most accurate breast cancer diagnosis (Chen et al., 2017; Choi et al., 2018; Dogan et al., 2018; Grimm et al., 2015; Harvey et al., 2016; Heacock et al., 2016; Machida et al., 2017; Mango et al., 2015; Moschetta et al., 2016; Oldrini et al., 2017, 2018; Panigrahi et al., 2017; Petrillo et al., 2017; Romeo et al., 2017; Strahle et al., 2017). Most of these studies used a wide range of patients who had normal, benign or malignant findings to compare both protocols and assess if cancer detection was maintained. The study by Leithner et al., (2019) evaluated all the different protocols used in a variety of studies and concluded that the abbreviated protocol maintained high diagnostic accuracy with a decrease in image acquisition and interpretation time. Leithner et al. (2019) addressed the fact that unnecessary breast biopsies may increase, however, sequences such as diffusion weighted imaging (DWI) are being investigated to be added to the abbreviated protocol to address this issue.

An abbreviated MRI protocol still needs refinement and standardisation, however it is expected that abbreviated breast MRI protocols will play an essential role in the future of breast imaging (Leithner et al., 2019).

1.3 Rationale to the study

To date, locally there is no general specific screening program for women who are at a high-risk of developing breast cancer. Due to the lack of programs available for these women, the probability is that such women may seek out screening on their own will in private clinics or hospitals, if they are able to afford it. In the local public hospital in Malta,

breast MRIs are performed for patients who have been diagnosed with breast cancer by mammography or as follow up of previous breast cancer diagnoses. The local hospital performs breast MRIs and has all the necessary resources to perform screening with MRI, therefore, this research study will investigate the possibility of using MRI to target the group of women who are at high-risk and offer what is considered to be the best breast cancer screening option in their case.

Even though breast MRI presents very encouraging results, breast MRI is a complex scan which can be difficult to implement (Leithner et al., 2019). However, with the improvements in the abbreviated breast MRI protocol, to date, eight different countries have started implementation of the abbreviated breast MRI exam (Leithner et al., 2019). There are a variety of abbreviated protocols which mainly consist of unenhanced and first contrast-enhanced T1- weighted sequences, while some of them additionally include T2-weighted, Short Tau Inversion Recovery (STIR), second contrast-enhanced, subtraction, and MIP images (Leithner et al., 2019). This study will select the adequate sequences for the abbreviated protocol and based on the study findings, provide recommendations for local implementation in the future.

1.4 Aim and Objectives

The aim of the study was to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging in the detection of lobular carcinoma.

The objectives of this research are outlined below:

- Based on literature findings, MR sequences from the full protocol were identified and selected for the abbreviated protocol.

- An MRI examination dataset was compiled for image review by radiologists. The MR dataset was composed of MR examinations with both positive and negative findings.
- The diagnostic accuracy and cancer yield of an abbreviated protocol was compared relative to the full protocol in terms of the breast imaging reporting and data system (BI-RADS) classification for interpretation of breast MRIs.
- The diagnostic accuracy was estimated using standard receiver operating characteristics (ROC) methods. The true disease status which is referred to as the *'gold standard'* was available for pathological correlation.
- The scores obtained through ROC analysis for both protocols were analysed.
- The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.
- Recommendations for the clinical use of an abbreviated MRI breast protocol based on the study findings were provided.

1.5 Research Methodology

The study adopted a quantitative, retrospective, and comparative non-experimental research approach by evaluating and comparing the current full MRI breast imaging protocol to an abbreviated MRI breast protocol.

The target population referred to the Magnetic Resonance (MR) breast images of patients who performed a breast MRI examination in Malta. Whilst the accessible population referred to MR breast images of patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this was when the most recent exams were performed using the full protocol on a 3-T Philips unit.

In this study the patient images used, were selected by using simple random sampling and the images were accessed by a radiographer acting as an intermediary on behalf of the researcher. A minimum of 2 radiologists specialised in breast imaging having a minimum of two years of experience in MRI breast reporting were conveniently selected to evaluate the diagnostic accuracy of an abbreviated protocol when compared to the full protocol. Images from the abbreviated protocol were presented to the radiologists who reviewed the images and filled in a data collection sheet for each set of images. The radiologists were blinded to the original radiological report, clinical history, other imaging modality reports and the number of negative and positive cases within the image dataset. The data collected from the abbreviated protocol was then compared with the data collected from the initial radiological MRI report based on the full MRI protocol. Lesions with a final BI-RADS category of 1 or 2 were considered as negative findings while those with a final BI-RADS of 3,4 or 5 were considered positive findings.

The findings were then compared with the gold standard being the histo-pathological correlation of a breast lesion or at least 12 months of negative findings on follow-up imaging with either mammography, ultrasound (US) or MRI in the absence of a biopsy.

1.6 Ethical considerations

Voluntary participation was obtained from the radiologists and the participants taking part in the study. All the images used were anonymised and the participants could not be identified, no personal data was collected to further ensure patient confidentiality. Prior to the start of the research process, ethical permission was sought and obtained from several entities as discussed in Chapter 3 Section 3.7.

1.7 Overview of the study

This research study is composed of the following sections:

Chapter One: provides a clear and concise introduction to the study along with an outline of the aim and objectives, rationale of the study and research methodology adopted.

Chapter Two: presents an analysis of the evidence-based literature in a critical manner and continues to discuss and assess this body of literature.

Chapter Three: provides a description and justification of the research methods used to address the research aim and objectives highlighted in Section 1.4, while also acknowledging the strengths and limitations of the study.

Chapter Four: presents and discusses the results and findings in relation to the theoretical body of literature reviewed in chapter two.

Chapter Five: presents conclusions and recommendations arising from this research study based on the results.

1.8 Conclusion

In this chapter the aims and objectives of the study were highlighted, together with the rationale for performing this research study. This chapter introduced the subject of breast cancer screening in high-risk women using an abbreviated MRI protocol. The next chapter will provide a critical analysis of the literature and relevant studies identified as well as an evaluation of their findings and results.

Chapter 2

Literature Review

2.1 Introduction

This chapter provides a review of the current literature, detailing information related to the study. The literature review serves to offer insight into the value of an abbreviated MRI protocol as an alternative especially for high-risk women. An overview of breast cancer incidence and mortality together with the types of breast cancer are presented. Furthermore, the risks of breast cancer are outlined, and the process of screening defined. Different breast cancer screening modalities are explored and compared to MRI. A critical review of the literature surrounding the MRI abbreviated protocol is provided along with the strengths and challenges when used for screening purposes. The literature is critically appraised enabling the researcher to identify any gaps in the literature which this research addressed.

2.2 Search strategy

All literature related to this study was retrieved from electronic searches. The researcher used several databases to identify relevant published studies which include Google Scholar, HyDi, PubMed (ncbi), Elsevier and SpringerLink. Electronic databases were more convenient since information was easy to retrieve plus literature related to health and medical institutions was more readily available online. Keywords and terms that were commonly used to look up data included breast cancer, screening, breast MRI, magnetic resonance imaging, abbreviated protocol, high-risk screening. Only peer-reviewed literature was selected, and studies published in the English language within the last 15 years. Additional studies were obtained by searching through the reference lists of relevant articles which is a technique referred to as '*snowballing*' (Wohlin, 2014).

The title and abstract of each article retrieved from the search was read and if relevant to the subject matter of the dissertation the article was downloaded. On evaluation of the identified literature, there was a vast amount of research regarding the abbreviated

protocol. A variety of studies have investigated the use of the abbreviated protocol for breast cancer screening purposes while others observed the abbreviated protocol for the assessment of known cancer lesions. Researchers have studied different abbreviated MRI protocols and efforts have been made to identify the most important sequences for breast MRI screening.

The sequences selected to form part of the abbreviated protocol and the data collection tool for this study, were based on the literature reviewed. The literature reviewed also helped the researcher choose the most appropriate design and method for this study.

2.3 Breast cancer

Cancer, as described by the World Health Organisation (WHO), is a generic term which encloses a group of diseases which can influence any part of the body. The characteristic feature of all cancers is that cells become abnormal and start to grow out of control to become the building blocks of tumours (Haussmann et al., 2020). Cancer cells tend to grow beyond their usual boundaries and invade adjoining cells and spread to other organs, this process is referred to as metastasis (WHO, 2022). As described by Zendehdel et al. (2018) '*breast cancer is a multifactorial disease'* and various factors will influence its occurrence. Early diagnosis and treatment can influence and shift the statistics (Nounou et al., 2015).

Eight million women worldwide were diagnosed with breast cancer between 2015-2020, making breast cancer the world's most prevalent cancer (WHO, 2021). Breast cancer accounts for more than 1 in 10 new cancer diagnoses each year worldwide (Alkabban & Ferguson, 2022). Breast cancer is the most common cancer and the most common cause of death among women (Momenimovahed & Salehiniya, 2019). In 2019 breast cancer accounted for 31.6% of newly diagnosed cancers in Malta (Malta National Cancer Registry, 2022).

2.3.1 Types of breast cancer

Breast cancer can start from the milk- producing glands (lobules) and in the cells lining the milk-producing glands (ducts), while a small number start from other tissues (Sharma et al., 2010). Breast cancer can be classified as either non-invasive (in-situ) carcinoma or invasive carcinoma (Nounou et al., 2015).

In non-invasive (in-situ) breast cancer, cells do not invade surrounding breast tissue but are confined to the ducts (Sharma et al., 2010). Non-invasive (in-situ) breast cancer is subclassified as ductal or lobular carcinoma (Nounou et al., 2015). As stated by WHO (2022), 85% of breast cancers arise from the ducts while the remaining 15% from the lobules. Non-invasive cancers are less common, with ductal carcinoma in situ (DCIS) occurring in1 in 5 (American Cancer Society, 2019). Lobular carcinoma in situ (LCIS) is rare and tends to be an incidental finding, found in a breast biopsy or surgical excision, therefore it is difficult to estimate the actual incidence of LCIS (Wen & Brogi, 2018).

In invasive breast cancer, cells break through the duct and invade surrounding breast tissue and may potentially spread to lymph nodes or distant organs such as brain, bones, lungs and liver (Akram et al., 2017). The most common invasive breast cancer originates from ductal or lobular cells and continues to invade and spread to other areas, unlike the non-invasive type, which remain contained. Invasive breast cancer, in rare cases, can also originate from other cells such as medullary carcinoma, mucinous carcinoma, tubular carcinoma, inflammatory breast cancer, Paget's disease and phyllodes tumours (Akram et al., 2017). Cancer of the breast can also be invasive without becoming metastatic (Sharma et al., 2010).

The most common type of breast cancer is invasive ductal carcinoma (IDC) and about 8 in 10 invasive breast cancers are IDC, while 1 in 10 are invasive lobular carcinoma

(ILC), the remaining are rare types of invasive breast cancers (American Cancer Society, 2019). In the year 2019 in Malta, out of 373 diagnosed breast cancers, 65 (17.4%) were DCIS, the rest were invasive breast cancers (Malta National Cancer Registry, 2022).

2.3.2 Breast Cancer Screening

Breast cancer evolves and progresses silently and can either be detected during routine screening or with symptomatic changes (Alkabban & Ferguson, 2022). Breast cancer screening will detect breast cancer at an early stage which would benefit substantially from therapy and improve prognosis. The main aim of screening in breast cancer, is to reduce the rate of breast cancer mortality through the early detection of the disease (Beau et al., 2018). Screening is a process which aims to identify women who harbour subclinical disease in a large population of individuals who do not (Kuhl et al., 2014).

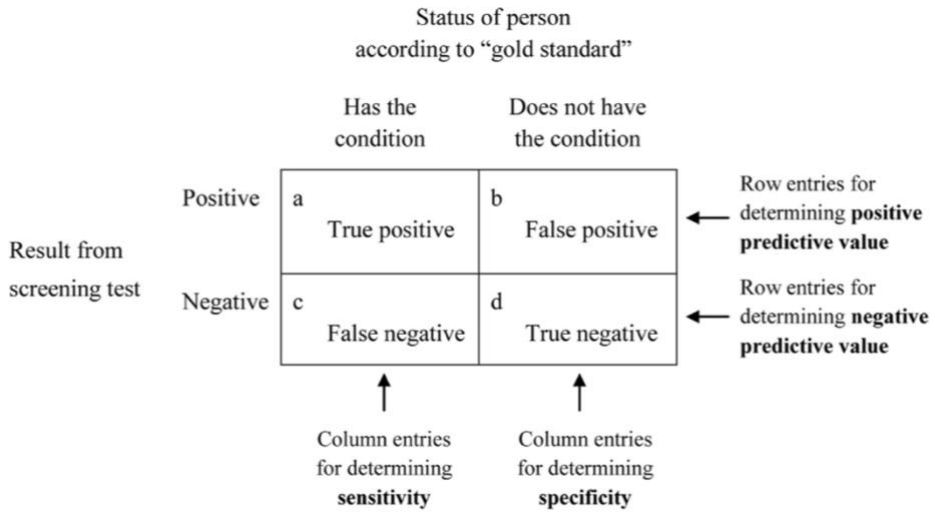
Every woman is at risk for breast cancer however, the level of risk is not the same for all women and ranges from very low to high. The risk depends on multiple risk factors some of which are modifiable, such as personal health history, while others are not, such as the individual's family history of breast cancer (Łukasiewicz et al., 2021). The person is categorised as being either low, average, or high risk depending on the number, type and combination of risk factors. Women who have an average risk of breast cancer are recommended to perform mammography screening. All women are encouraged to start mammography at the age of 40 years; however, different organisations provide their own recommendations based on literature findings.

Locally the Maltese national screening program invites women between the ages of 50-69 biennially for screening mammography. However, there have been proposals to start screening at the age of 45 years (Borg, 2022). Women who have an increased risk of breast cancer need consideration for breast screening to start at a younger age (<40 years) and have

more intense or frequent screening (Monticciolo et al., 2018). Locally, evaluations are still being made to introduce screening programmes for high-risk women (Ministry of Health, 2017). The imaging modalities that are available locally for breast imaging are mammography, handheld US, digital breast tomosynthesis (DBT) and MRI. Other imaging procedures such as contrast-enhanced digital mammography (CEDM) and automated whole-breast ultrasound (ABUS) are not available in the local hospital, with initial discussions taking place to consider the introducton of CEDM. ABUS however is available in the private sector.

2.4 Performance indicators

Performance indicators are essential to establish the accuracy of a health screening or diagnostic test (Trevethan, 2017). In health screening tests, it is essential to determine the power of a test to separate diseased from healthy individuals so that the findings are used for appropriate decision making (Baratloo et al., 2015; Trevethan, 2017). It is critical that the confidence of using a specific health screening test is justified, as there can be serious consequences for both the individual and the healthcare system (Trevethan, 2017). The predictive validity or power of a health screening test is compared with a definitive indicator which is referred to as the ‘gold standard’ of the same disease being evaluated (Figure 2.1) (Trevethan, 2017).



Key: **True positive (TP)** = the number of cases correctly identified as diseased
False positive (FP) = the number of cases incorrectly identified as diseased
True negative (TN) = the number of cases correctly identified as being healthy
False negative (FN) = the number of cases incorrectly identified as being healthy

Figure 2.1 The relationship of sensitivity, specificity, positive and negative predictive values (Trevethan, 2017)

2.4.1 Sensitivity

"*Sensitivity is the ability of a test to classify an individual as diseased*" (Parikh et al., 2008, p.45). A sensitivity of 100% reflects the ability of a test to detect all the people with the condition (Trevethan, 2017). The health screening test is being assessed on the basis of performance in relation to the 'gold standard', to assess if the health screening test is satisfactory (Trevethan, 2017). To estimate the sensitivity of a test, the proportion of true positives in the population of cases should be calculated as:

$$Sensitivity = \frac{True\ positive}{True\ positives + False\ negatives}$$

(Parikh et al., 2008)

2.4.2 Specificity

Specificity is defined as "*the ability of a test to classify an individual as disease free*" (Parikh et al., 2008, p.46). A specificity of 100% reflects the ability of a test to identify all the people who do not have the condition (Trevethan, 2017). Specificity assesses the ability

of a health screening test to correctly identify healthy individuals and not classify people as having a condition when they do not (Trevethan, 2017). To estimate the specificity of a test, the proportion of true negatives in a population of healthy individuals should be calculated as:

$$Specificity = \frac{True\ negatives}{True\ negatives + False\ positives}$$

(Parikh et al., 2008)

2.4.3 Positive Predictive Value (PPV)

The definition of PPV is "*the percentage of patients with a positive test who actually have the disease*" (Parikh et al., 2008, p.46) (i.e., identifying the true positives) while reducing individuals diagnosed as having the disease when they do not (i.e., avoiding false positives) (Safari et al., 2015; Trevethan, 2017). The higher the PPV is (closer to 100) suggests that the test is up to standard and as accurate as the 'gold standard' (Parikh et al., 2008).

$$PPV = \frac{True\ positive}{True\ positives + False\ positives}$$

(Parikh et al., 2008)

2.4.4 Negative Predictive Value (NPV)

The definition of NPV is "*the percentage of patients with a negative test who actually do not have the disease*" (Parikh et al., 2008, p.47) (i.e., identifying the true negatives) while reducing individuals diagnosed as healthy but actually having the disease (i.e., avoiding false negatives) (Safari et al., 2015; Trevethan, 2017). The higher the NPV is (closer to 100) then

this suggests that the test is up to standard and as accurate as the 'gold standard' (Parikh et al., 2008).

$$NPV = \frac{True\ negatives}{True\ negatives + False\ negatives}$$

(Parikh et al., 2008)

2.4.5 Other performance indicators

Cancer detection rate (CDR)- is the number of true positive examinations in the total number of screened individuals (per 1000 women) (Théberge et al., 2017; Lehman et al., 2017).

Recall Rate – is the number of positives (true positives and false positives) in the total number of screened individuals (Théberge et al., 2017). Recall rate is the portion of examinations which required further work-up such as further imaging or invasive procedures (e.g., biopsy) based on the findings of the initial screening test (Yankaskas et al., 2001).

2.5 Recommended screening guidelines for women at average risk

Throughout the years there have been numerous updates on the recommended screening guidelines, this is partially due to new data available together with advances or new imaging technologies. Some organisations such as American College of Radiology (ACR), American Cancer Society (ACS) and U.S Preventive Services Task Force (USPSTF), despite their differences, agree that mammographic screening commencing at 40 years of age saves the most lives (Arleo et al., 2017; Lee, Monticciolo & Moy, 2020; Monticciolo et al., 2021). All women should have the opportunity to begin early screening at the age of 40 years. Each organisation provides their recommendations, which are presented below in Table 2.1.

Table 2.1 Recommendations for Mammography Screening in Women at Average Risk for Breast Cancer (Elmore & Lee, 2020; Lee, Monticciolo & Moy, 2020; Sardanelli et al., 2017, ACOG, 2017)

Mammography	ACR, SBI, NCCN, NCBC, ASBrS	ACS	USPSTF, AAFP, ACP, WHO	ECIBC or EBC	EUSOBI	ACOG
Age	Recommend at 40 years	Offer at 40 years to 44 years, recommend at 45 years	Begin at 50 years, individual decision from 40 to 49 years	Begin screening at 45 years	Begin screening at 50 years of age, recommend at 40 years	Offer at 40 years, recommended by no later than 50 years
Interval	Annual	Annual from 40 to 54 years, biennial or annual for 55 years and older	Biennial	Biennial or Triennial at 45-49 years, biennial at 50-69 years and triennial at 70-74 years.	Annual for 40-49 years or biennial from 50 years and older	Annual or Biennial

Key: **ACR**-American College of Radiology, **SBI**- Society of Breast Imaging, **NCCN**- National Comprehensive Cancer Network, **NCBC**- National Consortium of Breast Centres, **ASBrS**- American Society of Breast Surgeons, **ACS**- American Cancer Society, **USPSTF**- United States Preventive Services Taskforce, **AAFP**- American Academy of Family Physicians, **ACP**- American College of Physicians, **WHO**- World Health Organization, **ECIBC**- European Commission Initiative on Breast Cancer, **EBC**- European Breast Cancer, **EUSOBI**- European Society of Breast Imaging, **ACOG**- The American College of Obstetrician and Gynaecologists

USPSTF suggests that biennial mammography screening begins at 50 years however, the individual may decide to start from 40-49 years and stop at 74 years as there is insufficient evidence of any benefit to continue after 75 years (Siu, 2016) (The local breast screening guidelines are discussed in Section 2.3.2). The growing interest in screening women at a younger age between 40-49 years was due to the sharp increase in incidence of breast cancer in women in this age group (Lee, Monticciolo & Moy, 2020). Lee, Monticciolo and Moy (2020) explained how annual screening of women between 40-49 years old came about because of the improvements in screening technology, increasing cancer detection and reducing false positives.

The European Breast Guidelines (EBG) or European Commission Initiative on Breast Cancer (ECIBC) generally agree with other guidelines such as American College of Physicians (ACP) however, diverge from others such as ACR on the frequency of screening since, EBG or ECIBC recommend biennial or triennial screening (Elmore & Lee, 2020). The ECIBC also suggest that screening can also be done using DBT instead of mammography. The EUSOBI together with 30 national breast radiology bodies issued recommendations for mammography screening (Sardanelli et al., 2017). The American College of Obstetrics and Gynaecologists (ACOG) provides recommendations to women, however, allows them to make their own decision after the potential benefits and harms are explained to them and the women's value and preference are taken into consideration (ACOG, 2017).

2.6 Recommended screening guidelines for women at high-risk

Breast cancer occurs all around the world however, the incidence, mortality and survival rates vary considerably between countries (Momenimovahed & Salehiniya, 2019). Risk or absolute risk is defined as the probability that an individual develops cancer over a specific period of time (Gail & Pfeiffer, 2005). Women in the general population have a lifetime risk of 12% for developing invasive breast cancer however, some groups of women carry an elevated risk (Conley, 2017). Classifying women based on the risk factors for breast cancer can design specifically targeted breast cancer screening programs which can improve early diagnosis in younger age groups (Momenimovahed & Salehiniya, 2019). Since screening in high-risk women starts at an early age, mammography is not ideal as there are concerns for young women to have an increased sensitivity to ionising radiation (Reeves & Kaufman, 2022). Screening breast MRI tends to be recommended because it will detect certain breast cancers without the added risk of radiation (Reeves & Kaufman, 2022)

Identifying the risk factors related with the increased prevalence of breast cancer development is essential in breast screening for women (Alkabban & Ferguson, 2022). Risk factors include anything that increases the individual's chance of getting a disease such as cancer (Feng et al., 2018). The study by Momenimovahed and Salehiniya (2019) identified seven factors that influenced the incidence of breast cancer in the general population. The seven factors include demographic factors, reproductive factors, hormonal, hereditary, breast related, lifestyle and others which include radiation and diabetes. The factors are divided into modifiable and non-modifiable risk factors (Vegunta et al., 2021). Hereditary, hormonal, reproductive and demographic factors are risk factors that cannot be modified however lifestyle factors such as diet, exercise, coffee, smoking, weight, alcohol and exogenous hormone therapy are all modifiable risk factors that can reduce the risk of breast cancer if modified (De Silva et al., 2019).

Certain women will have a higher risk of developing breast cancer due to coexistence of multiple risk factors or genetic variants (Vegunta et al., 2021). If a woman has a risk factor which is associated with a relative risk greater than one, then her risk of developing breast cancer will be higher than the average population, taking into consideration that all other things are equal (Joy et al., 2005). The National Comprehensive Cancer Network (NCCN) defines the high-risk population as women with a lifetime risk greater than 20% (National Comprehensive Cancer Network (NCCN), 2016). For this group of women, increased focus on breast cancer risk assessment and prevention is essential (Conley, 2017). The factors which classify a woman as high risk vary nationally and are based on expert panels (Hermann et al., 2020). According to the ACR Appropriateness Criteria high-risk women would have either one or a combination of the risk factors listed in Table 2.2.

Table 2.2 A list of high risk factors (Monticciolo et al., 2018)

High risk Factors
• Breast cancer gene mutations and other genetic syndromes such as Li-Fraumeni syndrome • Women with a history of chest irradiation between 10 and 30 years of age • Strong family history of breast cancer • History of lobular carcinoma in situ or atypia • Dense breasts • Personal history of breast cancer before 50 years of age

The ACS presents the same risk factors as the ACR for high-risk women (Saslow et al., 2007). While the ASBrS organization presents the same risk factors however divides women who had a history of breast cancer into two; if younger than 50 years or with dense breasts and 50 years or older with non-dense breasts (The American Society of Breast Surgeons (ASBrS), 2019). The NCCN guidelines subdivides high-risk categories according to age. Women with a strong family history or genetic predisposition who are <25 years, women ≥ 35 years of age with a five-year risk for invasive breast cancer >1.7% and finally women with prior chest irradiation who are younger or older than 25 years (Bevers et al., 2009). The NCCN guidelines do not consider women with dense breasts as high-risk unlike ACR, ACS and ASBrS (Bevers et al, 2009).

The ACR recommends that women at high risk should undergo risk assessment for breast cancer at the age of 30 years, so women who are at a higher risk are identified and may benefit from other forms of imaging besides mammography (Monticciolo et al., 2018).

2.6.1 Genetic mutations

Hereditary factors include any genetic mutations or family history of breast cancer which make women more susceptible to develop breast cancer. The genes *BRCA1* and

BRCA2 are primarily tumour suppressor genes (Kamińska et al., 2015). Large mutations in the coding sequences of BRCA genes will lead to hereditary syndrome referred to as Hereditary Breast/ Ovarian Cancer (Shiovitz & Korde, 2015). Thus, women who have cancer-predisposing mutations in *BRCA1* or *BRCA2* confer an increased risk in both breast and ovarian cancer (Saslow et al., 2007). Such mutations have an autosomal dominant pattern of transmission which causes the sister, mother or daughter of a woman with a BRCA mutation to have a 50% chance of carrying the same mutation (Saslow et al., 2007).

Women carrying the *BRCA1* or *BRCA2* gene have a lifetime risk of 65% to 80% and 45% to 85% respectively of developing breast cancer by the age of 70 years (De Silva et al., 2019). Feng et al. (2018) stated that the effect that the gene mutation has is related to the number of family members who have breast cancer, the more family members affected, the higher the risk of breast cancer. Several other genetic factors may contribute to breast cancer, *BRCA1* and *BRCA2* mutations being the most common and account for 40% of all hereditary breast cancer cases (Cobain et al., 2016). Inherited mutations in many other genes are less common and less drastic than BRCA mutations however, may also lead to breast cancer (Feng et al., 2018). Some of the mutated genes include ATM, TP53, CHEK2, PTEN, CDH1, STK11 and PALB2 (Feng et al., 2018). About 5% to 10% of all breast cancers and 20% to 25% of hereditary breast cancers are caused by *BRCA1/2* mutations (Balmaña et al., 2011; Paluch-Shimon et al., 2016). Primary prevention for women who carry the BRCA mutation is risk reducing mastectomies and/or chemoprevention (Trecate et al., 2006; Lee, Monticciolo & Moy, 2020). However, attention has moved towards a less radical approach that involves intensive surveillance including annual mammography and breast MRI which can significantly improve early detection of breast cancer (Trecate et al., 2006; Franceschini et al., 2019).

Considering the variations between recommendations from different organisations, there is consensus regarding the screening recommendations for women with high-risk genetic mutations (Lee, Monticciolo & Moy, 2020). As detailed in ACR, ASBrS, European Society for Medical Oncology (ESMO) and NCCN screening with annual MRI commencing at the age of 25 years of age with a combination of annual mammography starting at the age of 30 years (Bevers et al., 2009; Monticciolo et al., 2018; Paluch-Shimon et al., 2016; ASBrS, 2019). The ACS recommend annual mammography at the age of 30 years however no recommendation for or against MRI (Saslow et al, 2007). The ESMO and NCCN organisations suggest starting screening from the age of 25 years or 10 years before the youngest case in the family, depending which is earlier (Bevers et al., 2009; Paluch-Shimon et al., 2016).

Genetic testing is recommended for early detection and/ or prevention of breast cancer (Feng et al, 2018). The ACS recommends that genetic testing for *BRCA1* or *BRCA2* is offered to adult members of families with a known BRCA mutation and to women who have 10% likelihood of carrying this mutation (Saslow et al, 2007).

2.6.2 Family history

Family history is a well-known risk factor for the increased onset of breast cancer (Liu et al., 2021) depending on the degree of family history. A large number of women in the general population have at least one close relative with breast cancer however, this does not increase the risk for a woman to develop breast cancer (Saslow et al., 2007).

Women with family history of two or more relatives having had breast cancer have a 2.5 fold increased risk of breast cancer (Brewer et al., 2017). A woman having only one or two first-degree relative/s (mother, sister or daughter) with breast cancer doubles and/or triples the risk respectively (Feng et al., 2018). The risk is also increased if a woman has a

father or brother with breast cancer (Feng et al., 2018). Breast cancer risk increases when close relatives develop breast or ovarian cancer at a young age. Women without any genetic mutations have a 14.1% risk of developing breast cancer when first-degree relatives develop breast cancer before 40 years of age (Liu et al., 2021). The ASBrS recommends annual MRI with concurrent mammography for women who have a strong family history starting at the age of 35 years of age (ASBrS, 2019). While NCCN screening recommends the same concurrent screening program starting in women aged 25 years and older (Bevers et al., 2009). The ACR and ACS provide no specific age at which annual mammography and MRI should start (Monticciolo et al., 2018; Saslow et al., 2007). The ACS recommends the use of models that include first and second degree family history (e.g: Claus or BRCAPRO) to determine eligibility for screening breast MRI (Monticciolo et al., 2018). According to Monticciolo et al, (2018) MRI performed better in patients with a history of breast cancer rather than women with a strong family history due to fewer false positives, higher specificity, equivalent sensitivity and cancer detection rate (CDR).

2.6.3 History of chest irradiation

Women who in the past were treated with chest therapy for another cancer when they were young, such as Hodgkin's lymphoma, have a higher risk of developing breast cancer (Feng et al., 2018). The risk starts approximately 8 years following the completion of radiation therapy (Lee, Monticciolo & Moy, 2020). Women treated with chest radiation (cumulative dose of 10 Gy or greater) as a teen or young adult (<30 years old) have a higher risk of developing breast cancer since the breasts would still be developing when irradiated (Feng et al., 2018). Treatment with radiation after the age of 40 years does not provide a significant increase in breast cancer risk (Feng et al., 2018). Around 20% of these women may develop cancer by the age of 40-45 years (Lee, Monticciolo & Moy, 2020). More advanced treatments have used lower doses of radiation and limited-field radiotherapy which

significantly reduces direct breast radiation and thus lower breast cancer risk (Hilal & Rudy, 2016).

The NCCN and ACR recommend annual mammography and MRI screening starting at the age of 25 years or 8 years following radiation whichever comes later (Bevers et al., 2009; Monticciolo et al., 2018). While ASBrS recommends annual MRI starting at the age of 25 years with concurrent mammography starting at 30 years of age (ASBrS, 2019). The ACS recommends annual mammography at 30 years of age and MRI screening due to the high risk of secondary breast cancers in this group (Saslow et al., 2007).

2.6.4 Personal history of breast cancer

Women with a personal history of breast cancer are classified as high-risk. Personal history of breast cancer increases the risk for recurrence or for a second primary breast cancer (Monticciolo et al., 2018). The meta-analysis by Darby et al. (2011) found that the risk of recurrence during the first 10 years following diagnosis is 19.3%, which is significantly higher than that of the general population. Women who are diagnosed with breast cancer before the age of 50 have a 20% or more lifetime risk of developing another breast cancer (Punglia & Hassett, 2010). Women with a history of breast cancer have a 0.5%- 1% risk per year of developing breast cancer in the contralateral breast (Monticciolo et al., 2018). Oestrogen receptor positive breast cancers increase the risk of developing another cancer in the future (Monticciolo et al., 2018). Such women present a higher risk than having a strong family history (Monticciolo et al., 2018).

The sensitivity of mammography was found to be low in women with a history of breast cancer due to postsurgical scarring and dystrophic calcifications (Lee, Monticciolo & Moy, 2020). The study by Mann et al. (2019a) found MRI produced sensitivities which ranged from 80-100% while mammography ranged from 0-53%. MRI performed better in patients who had a history of breast cancer rather than family or genetic history, as there

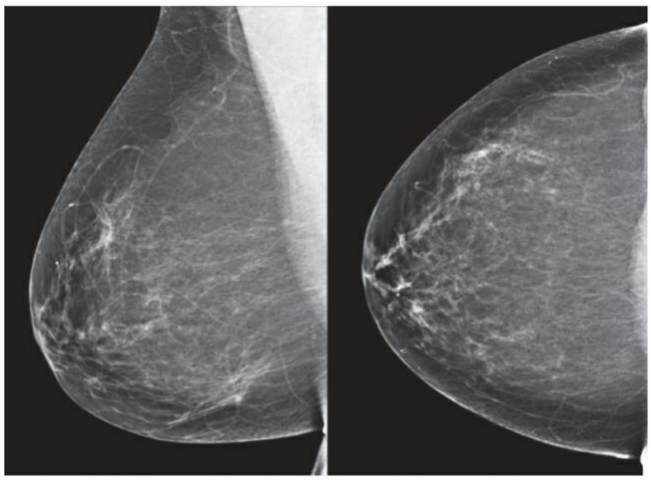
were lower false positives, better specificity, and equivalent sensitivity and cancer detection rates (Lehman et al., 2016). The findings by Lehman et al. (2016) supported the use of MRI for such women since MRI can detect mammographically occult invasive breast cancers while they are still small and node negative. The ACR recommends the use of annual MRI in conjunction with mammography for women diagnosed before the age of 50 years (Monticciolo et al., 2018). The ACS supports annual screening with mammography starting at the age of 30 years however, it is argued that there is insufficient evidence to recommend for or against MRI (Saslow et al., 2007). The ASBrS divides women with personal history based on age and the density of the breast (ASBrS, 2019). Women younger than 50 years or with dense breasts are recommended to have both annual MRI and mammography however, women older than 50 years or with non-dense breasts are recommended to have an annual MRI but there is no recommendation for or against MRI (ASBrS, 2019). The NCCN recommends annual mammography for surveillance following the history of breast cancer (Modi et al., 2020). There is a lack of agreement between the organisations regarding the use of MRI for surveillance in women with a personal history of breast cancer, this is due to the lack of evidence available on the use of MRI in such women (Lehman et al., 2016). Locally women who have a history of breast cancer have routine follow up with mammography or MRI and in certain types of breast cancers even both concurrently.

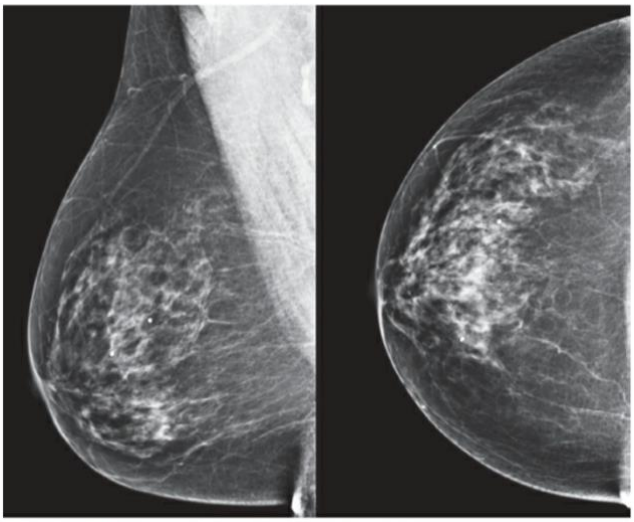
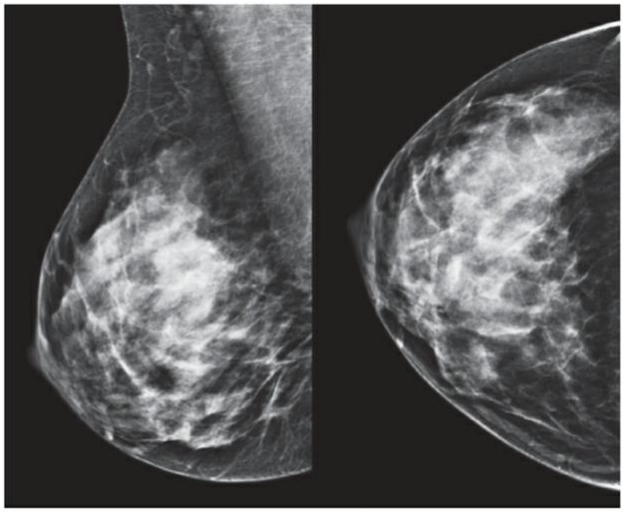
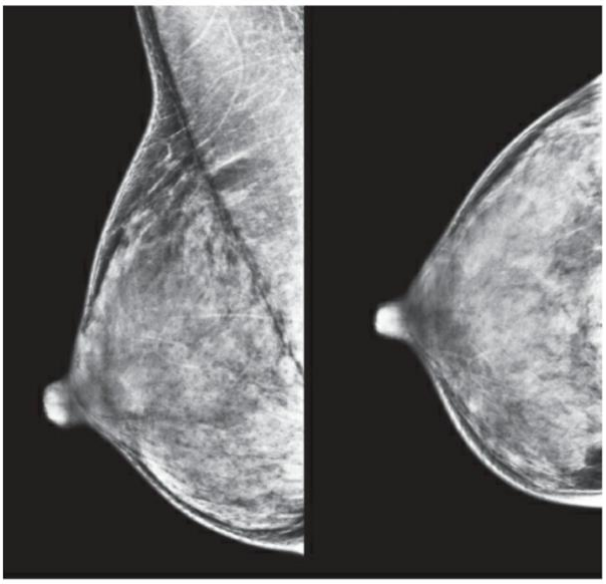
2.6.5 Dense Breasts

Breast density has been revealed to be a strong independent risk factor for breast cancer (Bravi et al., 2018; Duffy et al., 2018; Mann et al., 2022). Mammographic appearance of a breast depends on the different attenuation characteristics of the breast tissue components (Pinsky & Helvie, 2010). The breast is mainly made up of various amounts of fibrous and glandular tissue together with fatty tissue. Fibrous and glandular tissue absorb the x-ray beam much more than fat therefore fewer x-rays reach the detector resulting in a

whiter (radiopaque) appearance (Pinsky & Helvie, 2010). Whilst in fatty tissue more x-rays penetrate and therefore reach the detector making fat appear dark (radiolucent) on a mammogram (Pinsky & Helvie, 2010). Mammographic breast density is the representation of the amount of fibrous and glandular tissue (radiopaque) in the breast in relation to fatty tissue (radiolucent) (Pinsky & Helvie, 2010). According to the ACR BI-RADS atlas terminology, mammographic density is classified into four density categories as displayed in Table 2.3 (D'Orsi et al., 2013). The latter two categories classify a woman as having 'dense' breasts (Mann et al., 2022).

Table 2.3 Breast tissue density category (D'Orsi et al., 2013)

Breast Category	Breast Composition	Image Reference
A	Almost entirely fatty	

B	Scattered areas of fibro glandular density	
C	Heterogeneously dense	
D	Extremely dense	

As stated by Pinsky and Helvie. (2010), having extremely dense breasts is a risk factor for breast cancer, yet it is not acknowledged in current risk assessment models. The risk for breast cancer is four to six times higher in women with dense breasts (Weigel et al., 2016). Breast cancer appears white on a mammogram irrelevant of the type (mass, calcification, distortion, etc.) therefore the possibility that a cancer is masked by overlying breast tissue is much greater in women who have dense breasts (Freer, 2015; Pinsky & Helvie, 2010). Mammography is less sensitive in dense breasts as it is a two-dimensional summation image were all breast tissue is overlapping therefore, there is a substantial amount of cancers being missed / not diagnosed especially in dense-breasted women (Chen et al., 2015; Freer, 2015; Pinsky & Helvie, 2010).

Besides having the risk that breast cancer is masked and thus not detected, women who have dense breasts undergoing mammography have an increased risk of developing breast cancer due to a high amount of fibroglandular tissue present within the breast and the breast composition (Wanders et al., 2018). Cancers most commonly rise from the epithelial tissue, thus a large amount of epithelial tissue would increase the chance that cancer may arise in this tissue (Freer, 2015). Thus, women with dense breasts have a high risk of developing breast cancer and a low chance of detecting it with mammography. In dense breasts the sensitivity of mammography decreases from 86-89% to 62-68% (Al-Mousa et al., 2020; Mann et al., 2022). The increased risk for breast cancer and masking effect in mammography act together to increase the interval breast cancers i.e. cancers which become clinically visible between two rounds of screening (Mar et al., 2019, Mootz et al., 2019).

Density tends to change over a woman's lifetime under certain influences such as age, menopausal status and hormone replacement therapy (HRT) (Mandelson, 2000). Menopause in a woman tends to alter the glandular breast tissue and reduce the density therefore a decrease in breast density with increasing age is expected (Checka et al., 2012).

Fifty percent of women between the ages of 25 and 49 years have dense breasts (>50% density-BI-RADS C) (Pinsky & Helvie, 2010). Dense breasts are observed in women who are pre-menopausal and who are not included in the screening program unless they are classified as high risk for breast cancer and have to start screening at a younger age (25 or 30 years old) (Pediconi et al., 2009). With increasing age the breast density tends to decrease unless there are other factors such as HRT which would influence breast density (Carney et al., 2003). HRT has an effect on the breast density therefore, indirectly causes an increased risk for breast cancer, making breast density the mediating factor (Byrne et al., 2017; Rice et al., 2016). Hormone therapy tends to slow down the expected age-related decrease in breast density. Post-menopausal women who never used such therapy had a greater decline in breast density after the age of 50 years when compared with women who used or are currently using it (Kelemen et al., 2008).

Due to the limitations of mammography as a screening tool for women with dense breasts, underdiagnosis is expected in women with extremely dense breast tissue compared to other women (Mann et al., 2022). The study by Freer (2015) observed a sensitivity of 86-89% for mammography in fatty breasts while a 62-68% sensitivity in extremely dense breasts. The study by Carney et al. (2003) found similar results and obtained a sensitivity of 87% for fatty breast types whilst 62.9% for extremely dense breast. MRI is not influenced by breast density as it does not suffer from any tissue overlapping as mammography and can hence measure more density related biological properties than mammography (Chen et al., 2015). The DENSE trial has provided promising research with regards to the use of MRI in women with extremely dense breasts. The use of supplementary MRI screening reduced the rate of interval cancers by 84%, which in turn reduces underdiagnosis (Bakker et al., 2019). The diagnostic accuracy of mammography in women with dense breasts has improved, however is still as low as 70% (Albert et al., 2015). Recommendations for screening with

MRI for dense breasts is somewhat vague. Certain organisations such as ACS who have dated guidelines do not have any recommendations for or against MRI but recommend mammography for women with dense breasts starting at the age of 30 years (Saslow et al., 2007). The most recent guidelines from ACR and NCCN suggest MRI in dense breasts especially when combined with other risk factors (Lee, Monticciolo & Moy, 2020). The European Society of Breast Imaging (EUSOBI) has relied on the evidence from the meta-analysis by Marmot et al. (2013) that women with extremely dense breasts between the ages of 50 to 70 years to be screened using MRI (Mann et al., 2022). The ACR and ASBrS suggests annual screening with both MRI and mammography for women with dense breasts who have had a history of breast cancer (ASBrS, 2019; Monticciolo et al., 2018). The NCCN does not consider dense breasts as a risk factor that categorises women as high-risk (ASBrS, 2019). Locally, evaluations are still being made to introduce specific programmes for women who have dense breasts (Ministry of Health, 2017). Currently, the procedure is that if a mammogram is difficult to interpret due to dense breasts, then the radiologists will tend to recall the patient for an US.

2.6.6 Atypical Epithelial Hyperplasia

Women with benign proliferative diseases such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and LCIS have an increased risk of 3-10 times more of developing breast cancer when compared with the general population (Bevers et al., 2009; Lee, Monticciolo & Moy, 2020). Women with LCIS and atypical epithelial hyperplasia have lifetime risk estimates ranging from 10 to 20% (Arpino et al., 2005). Women with LCIS have a risk of subsequent development of cancer in both breasts up to 15 years after initial diagnosis (Monticciolo et al., 2018). The risk related to ADH is also increased but lower than LCIS (Monticciolo et al., 2018). Having these diseases makes a women classified as high-risk and organisations such as ACR recommend annual

mammography and annual MRI especially if other risk factors are present (Monticciolo et al., 2018). The ACS recommends annual mammography starting at 30 years of age however there are no recommendations for or against MRI (Saslow et al., 2007). The NCCN recommends annual mammography and annual MRI in conjunction with mammography for LCIS (Bevers et al., 2009). The ASBrS includes women who have LCIS, ADH or ALH in the subgroup of women with a lifetime risk of 20 % or more and recommends annual mammography and additional MRI at the age of 35 years if recommended by their physician (ASBrS, 2019).

2.7 Breast cancer screening imaging modalities

2.7.1 Mammography

For a screening test to be effective it must be safe to administer, cost-effective, widely available, have a high detection rate and improve health outcomes. Mammography meets all these requirements (Seely, 2017). Digital x-ray mammography has been the screening tool used to detect breast cancer for several decades throughout the world (Deike-Hofmann et al., 2019; Greenwood, 2019). Mammography is the most cost-effective tool for breast cancer screening (Chhor & Mercado, 2017). Mammography is the current gold standard screening tool and is the only imaging modality which was proven to decrease breast cancer mortality rates by 25% to 40% (Mootz et al., 2019). In 2014, experts from 16 countries concluded that women who attend regular mammography screening between 50 and 69 years of age will have a 40% reduction of breast cancer mortality (Lauby- Secretan et al., 2015). Many randomized trials and observational studies agreed and stated that mammography screening reduces breast cancer mortality by 30% or more (Tabár et al., 2015; Monticciolo et al., 2021; Webb et al., 2014). While mammography remains the mainstay in routine breast cancer screening it is "*far from perfect*" (Chhor & Mercado, 2017, p.284), due to a sensitivity as low as 70 % which could result in the reduced detection of

cancers (Chhor & Mercado, 2017; Deike-Hofmann et al., 2019). Limitations in sensitivity and specificity persist even with recent technological improvements (Pacilè et al., 2020). The number of advanced breast cancers have not decreased with the implementation of breast screening programs (Bleyer & Welch, 2012; Welch et al., 2016). However, in the last three decades early stage invasive breast cancer and ductal carcinoma in situ detection has increased (Warrier et al., 2016). Points of criticism have also been raised against mammography screening due to the fact that in spite of long standing mammography screening, breast cancer still remains the major cause of cancer death among women (Kuhl, 2018). Such information has led to claims that mammography may over-diagnose small in situ or indolent invasive cancers while failing to detect more aggressive breast cancers (Greenwood, 2019; Kuhl, 2018; Mootz et al., 2019). Cancers can have imaging appearances that make the detection by mammography difficult or render them indistinguishable from normal or they are mistakenly diagnosed as benign. (Kuhl, 2018). For example, a biologically aggressive high-grade cancer, not detected by mammography was however, detected on MRI (Figure 2.1 and 2.2). The sensitivity of mammography is limited mainly due to dense breasts and the tumour growth pattern which make detection difficult or suggestive of benign disease (Kuhl, 2019; Mootz et al., 2019; Roganovic et al., 2015). The decrease in sensitivity of mammography is intensified in young women with dense breasts and thus in women who are at a high risk of developing breast cancer mostly BRCA 1 and BRCA 2 mutation carriers (Chhor & Mercado, 2017; Deike-Hofmann et al., 2019; Mootz et al., 2019). Therefore, mammography is limited in its usefulness in high-risk younger women (Drukteinis et al., 2013).

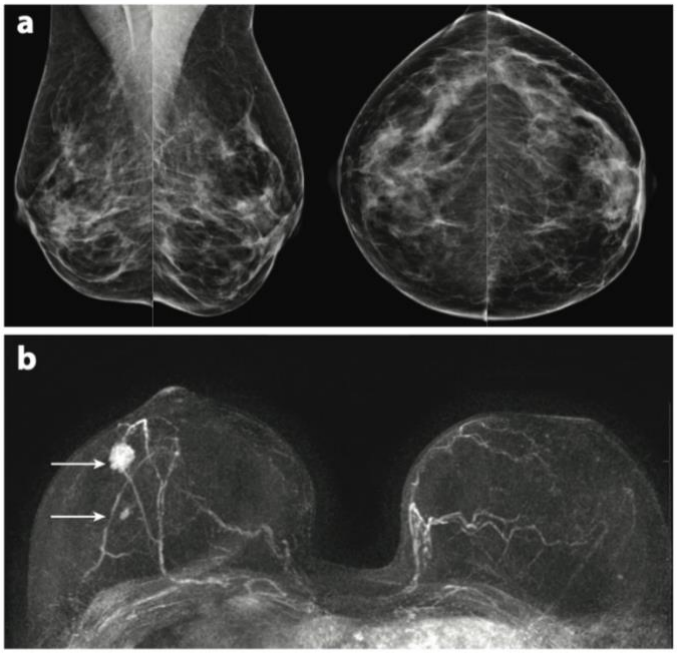


Figure 2.2 Example of a mammography-occult biologically aggressive cancer (a) two-view mammography with no evidence of breast cancer. (b) Two enhancing lesions present in an abbreviated MRI (biopsy proven- multifocal high grade HER 2-positive) (Kuhl et al., 2019).

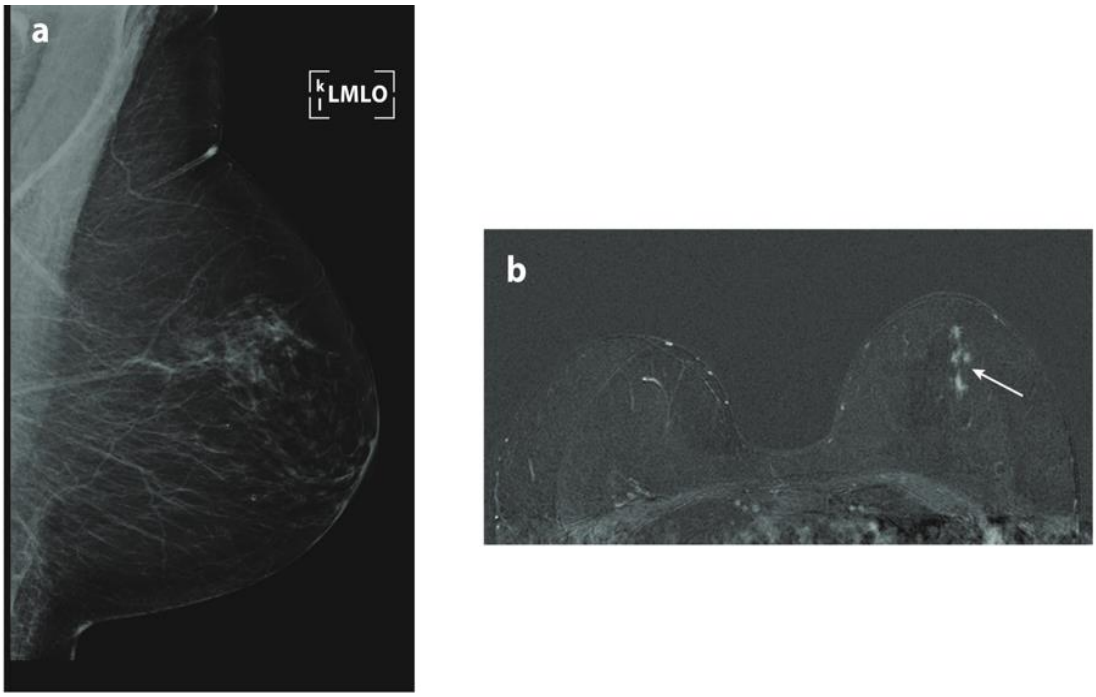


Figure 2.3 Example of a mammography-occult biologically aggressive cancer (a) Mammography with no evidence of breast cancer or dense breasts. (b) Ductal enhancement present in an abbreviated MRI (biopsy proven- high grade DCIS) (Kuhl et al., 2019).

2.7.2 Magnetic Resonance Imaging (MRI)

MRI in its current use does not fulfil the criteria of a screening test, as it is not cost effective, neither rapid nor easily applied (Kuhl, 2019). However, out of all the available imaging modalities, MRI offers the highest diagnostic accuracy and sensitivity for the detection of breast cancer, irrespective of stage, type of cancer and breast density (Chhor & Mercado, 2017; Kuhl, 2019; Riedl et al., 2015). MRI offers a higher cancer detection rate over mammography, DBT and US and is undisputedly the most sensitive imaging modality for breast cancer (Leithner et al., 2019; Mootz et al., 2019). MRI does not only have a high sensitivity but also has the capability of detecting cancers less than 1 cm in size when compared with mammography and US (Sardanelli & Podo, 2007; Leach et al., 2005; Warner et al., 2004).

MRI is a non-invasive imaging technique which does not make use of any radiation (Ghadimi & Sapra, 2019). A 3T magnet is used for breast imaging with a specialized breast coil used to obtain images. The patient would be in a prone position with the breasts positioned through openings in the coil (Figure 2.3). Gadolinium contrast medium (0.1mmol/kg) is administered intravenously with a power injector. The administration of contrast is used in almost all breast MRI examinations except for evaluation of silicone implants (Gunduru & Grigorian, 2021). Breast MRI should ideally be performed between day seven to day 14 of the menstrual cycle to reduce the effect that hormones have on background parenchymal enhancement and thus reduce the rate of false positives (Gunduru & Grigorian, 2021).

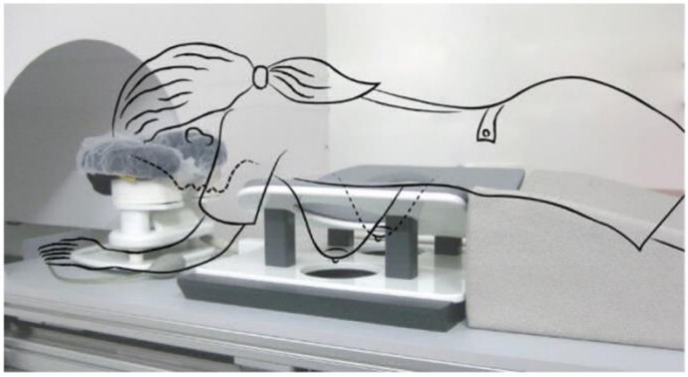


Figure 2.4 An illustration of patient positioning in breast MRI (Nissan et al., 2014)

The demonstration of contrast enhancement is the basis of breast cancer detection in MRI which is caused by the angiogenic activity of cancers (Kuhl, 2019). The process of angiogenic activity leads to a fast arterial-type enhancement at the area of breast cancers (Kuhl, 2019). The high sensitivity produced by MRI is due to the unmatched soft-tissue contrast and functional information provided by MRI scans in conjunction with the correlation of angiogenic activity of cancers (Sung et al., 2016). Breast MRI is not influenced by age, breast density or any genetic mutations therefore, any biologically relevant breast cancers are detected (Riedl et al., 2015). Breast MRI has traditionally been used as a second-line imaging modality to diagnose equivocal findings on mammography or US (Kuhl et al., 2014). However, over the past decade, the consideration of breast MRI for screening has increased greatly (Kuhl et al., 2014). The costs and lack of availability contribute to MRI being greatly underutilised even in women at high-risk who need it the most (Kuhl, 2019). An abbreviated MRI protocol was set up by Kuhl et al. in 2014 to counteract the limitations of time and cost presented by the full protocol, which provided very promising results. A detailed discussion on the abbreviated breast MRI protocol is found in Section 2.8.

Screening with MRI was initially recommended for women who have more than 20% lifetime risk of developing breast cancer, to help improve cancer detection and reduce

interval cancers i.e. cancers which become clinically visible between two rounds of screening (Leithner et al., 2019, Mootz et al., 2019, Mann et al., 2015; Sardanelli et al., 2010; Saslow et al., 2007). MRI used in high-risk women reduces the interval cancers due to its high sensitivity and more lower stage breast cancers are detected rather than aggressive cancers (Kuhl et al., 2014). For women with high-risk of developing breast cancer, MRI was found to be cost effective (Taneja et al., 2009) however there are still studies on going for the use of MRI for women at moderate or low risk (Leithner et al., 2019; Mann et al., 2019b). The advantage about MRI screening is the low or even absence of interval cancer (Kuhl, 2019). A low interval cancer rate was observed for both women at high-risk and average risk with MRI screening. This indicates that with appropriate imaging methods interval cancers can be reduced or avoided altogether unlike in mammography where the interval cancer rate is due to underdiagnosis (Kuhl, 2019).

Mango et al. (2019) explained how the detection of more cancers with MRI tends to raise concern for the potential overdiagnosis of breast cancer. When Saadatmand et al. (2019) compared MRI with mammography for women with familial risk, more breast cancers were detected in MRI compared to mammography even though there was no difference in the incidence of breast cancer. Mammography detected more late stage and node-positive cancers which shows that MRI can potentially decrease mortality compared to mammography (Saadatmand et al., 2019). Roca et al. (2020) emphasised how MRI detects more invasive cancers than mammography which detects more DCIS. Almost half of the cancers detected with MRI in the study by (Kuhl et al., 2017) corresponded to differentiated high-grade lesions. MR imaging enables the early detection of cancers which if remained undetected would develop into more advanced interval cancer or ultimately become mammographically visible (Kuhl et al., 2017). This inherently introduces the potential for MR imaging to diagnose only indolent cancers and therefore bring about overdiagnosis

(Kuhl et al., 2017). Kuhl et al. in 2019, argued that MRI not diagnosing low-grade DCIS would essentially help to avoid overdiagnosis.

2.7.3 Other imaging modalities

Other imaging modalities used for the detection of breast lesions include US or ABUS and DBT and CEDM.

DBT makes use of multiple projections acquired across an arc which are then reconstructed into a series of stacked images (Chong et al., 2019). DBT is a technique which allows for a 3-D examination of the breast reducing the superimposition of breast tissue which in-turn may reduce the masking effect (Chen et al., 2015). Comstock et al. (2020) stated that DBT was initially used to complement mammography, however, DBT has increasingly replaced mammography.

There is a lack of literature regarding the use of DBT in high-risk women as generally studies focus on the use of DBT in women with dense breasts. Women who are at increased risk for developing breast cancer are young with dense breasts therefore, the results of such studies may be beneficial for such women. The study by Phi et al. (2018) evaluated 16 cases who had both DBT and mammography and reported that DBT improved cancer detection rate in women with dense breasts when compared with mammography. DBT allows for a 3-D examination of the breast reducing the superimposition of breast tissue which in-turn reduces the masking effect (Figure 2.4) (Chen et al., 2015; Coop et al., 2016).

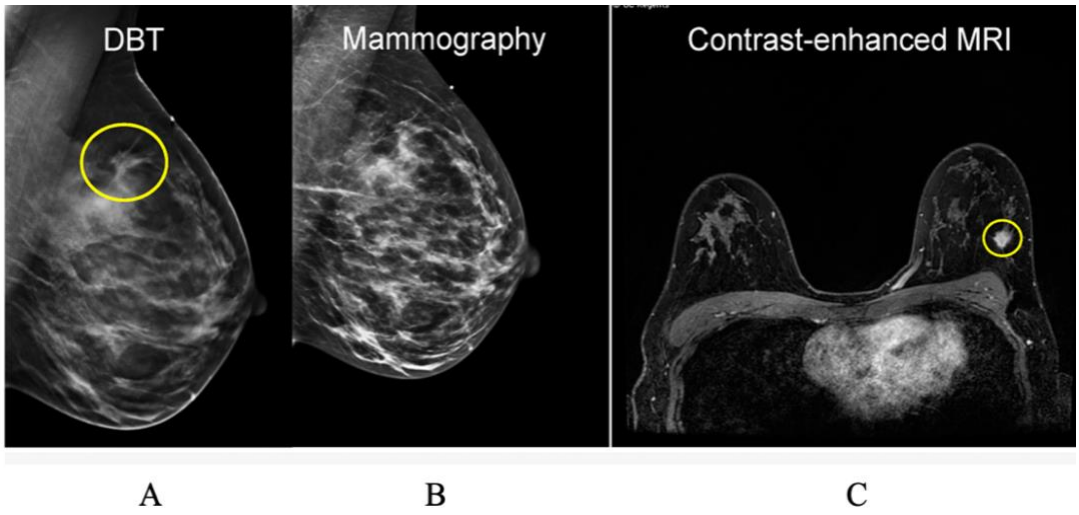


Figure 2.5 Example of a mammography-occult biologically aggressive cancer visible on DBT and MRI (a) DBT with evidence of breast cancer with asymmetry and architectural distortion. (b) Dense breast tissue obscuring the findings on mammographic image (c) Invasive ductal carcinoma present in the contrast-enhanced MRI (Jones et al., 2020).

Handheld US in breast imaging is generally used to complement mammography to confirm the nature of masses observed on a mammogram. However, adding US to mammography can help to identify mammographically occult breast cancer (Mar et al., 2019). There are more studies that investigated the use of US in women with a high risk of breast cancer unlike DBT (Berg et al., 2012; Cortesi et al., 2019; Wang et al., 2019). The ACR and SBI recommend the addition of US to mammography in women with a high risk of developing breast cancer who cannot undergo MRI due to contraindications (Cortesi et al., 2019; Warrier et al., 2016). The American College of Radiology Imaging Network (ACRIN) 6666 trial evaluated the use of US in women who have a high risk of breast cancer, this multicentred study identified 3.7 additional cancers per 1000 screens. (Berg et al., 2012). Wang et al. (2019) observed a satisfactory diagnostic yield for US in high-risk women. The study by Cortesi et al. (2019) divided the women into different risk groups: BRCA, high risk, intermediate risk and slightly increased risk, and studied the effect of US in each group. The addition of US to mammography in high-risk women improved the sensitivity to 100%, thus Cortesi et al. (2019) suggested that in this group it is justified to enhance screening with

US. The sensitivity of US for BRCA carriers was 22.7% however, in this population MRI produced a 94% sensitivity which superseded US (Cortesi et al. 2019).

ABUS is a new imaging technique which is an additional screening tool specifically for women with heterogeneously and extremely dense breasts (Boca et al., 2021). The ABUS is a volumetric sonographic technique which has a large transducer that is placed on the patient's entire breast, providing multiplanar reconstructions of the breast (Mussetto et al., 2020). The ABUS has a comparable diagnostic accuracy to handheld US (Kim et al., 2020; Rella et al., 2018). ABUS is a reproducible tool in the description of lesion location, distance from nipple and size (Rella et al., 2018).

Contrast-enhanced digital mammography (CEDM) combines digital mammography with the intra-venous administration of iodinated contrast medium (Ghaderi et al., 2019). CEDM images are obtained after contrast administration to assess breast tissue function similar to MRI (Hashem et al., 2021; Vegunta et al., 2021). CEDM imaging is relatively new and has a superior diagnostic performance when compared with mammography, US and DBT, with comparable results to MRI (Hashem et al., 2021). Hashem et al. (2021) concluded that CEDM is a valuable imaging modality in women who are at high-risk for breast cancer compared with mammography which has a lower cancer detection rate. In the study by Sung et al. (2019) it was stated that CEDM has the potential to replace 2-D mammography in high-risk women. The sensitivity of CEDM was 87.5% which is much higher than 50% for mammography (Sung et al., 2019). Hashem et al. (2021) insisted that CEDM deserves similar attention as MRI and further studies are required to validate the positive results achieved from this imaging examination. CEDM is currently recommended to be used in women who have contraindications to MRI (Ghaderi et al., 2019; Vegunta et al., 2021).

2.8 Abbreviated breast MRI protocol

MRI of the breast is "*undisputedly the most sensitive of image methods to detect cancer*" (Leithner et al., 2018, p.85). The application for MRI in breast screening has not been implemented since MRI is expensive and time consuming therefore making it less available when compared with conventional imaging (Leithner et al., 2018). Kuhl et al. (2014) aimed to create the concept of breast MRI screening similar to mammographic screening by setting up the concept of an abbreviated breast MRI protocol. The aim of the abbreviated protocol was to overcome the limitations and increase access to screening breast MRI by reducing the scanning time and reading time whilst maintaining the same diagnostic accuracy to the full protocol (Kuhl et al., 2014). Following in the steps of Kuhl et al. (2014), several studies have investigated different abbreviated protocols with similar results presented in Table 2.4. The principle of an abbreviated MRI protocol is to design a protocol that is tailored to answer a single clinical question, whether there is the presence or absence of breast cancer (Kuhl, 2019). The concept of a fast abbreviated MRI protocol is very appealing due to its high diagnostic accuracy with a reduction in costs as the value of healthcare is the women's outcome over costs (Leithner et al., 2018). Abbreviated MRI has gained superiority over other imaging modalities throughout the years however it still has its own weaknesses (Pham et al., 2020). The study by Pham et al. (2020) analysed the abbreviated MRI protocol and established its strengths and weaknesses, which will be discussed in Section 2.9 and 2.10 respectively.

2.8.1 Different types of abbreviated breast MRI protocols

Following the initial study by Kuhl et al. (2014) there have been more studies regarding the application of the abbreviated MRI protocol and efforts have been made to identify the sequences necessary to provide the most confident breast cancer diagnosis (Leithner et al., 2019). An MRI abbreviated protocol should contain the minimum number

of sequences required for detecting any suspicious lesions (Mootz et al., 2018). While the full diagnostic MRI protocol is reserved for further characterisation of suspicious lesions to differentiate between benign from malignant disease with the aim to prevent false- positives and false- negatives (Mootz et al., 2019). Greenwood et al. (2019) explained how an abbreviated MRI protocol does not require any specific sequences to be used, it depends on the individual organisation to decide however, the scanning time should be less than 10 minutes. Currently there are no criteria or time limits of an exam to define an MRI protocol as abbreviated (Mann et al., 2019c).

Table 2.4 Abbreviated protocol used in 17 studies

Study with reference	Abbreviated Protocol 1	Abbreviated Protocol 2	Abbreviated Protocol 3
(Kuhl et al., 2014)	-Axial unenhanced T1-weighted imaging (not fat sat (FS)) -Axial first contrast enhanced T1 weighted imaging (not FS) - subtraction and MIP		
(Mango et al., 2015)	-Sagittal Unenhanced T1-weighted imaging (FS) -Sagittal First contrast-enhanced T1-weighted imaging (FS) -Subtraction, MIP		
(Grimm et al., 2015)	-Axial T2-weighted imaging (FS) -Axial unenhanced T1-weighted imaging (FS) -Axial first contrast-enhanced T1-weighted imaging (FS) (All sequences were taken in the axial plane, but readers could reconstruct images in the sagittal and coronal plane)	Abbreviated protocol 1 + Second contrast-enhanced T1-weighted imaging (FS)	
(Harvey et al., 2016)	-Axial unenhanced T1-weighted imaging (FS) -Axial post contrast-enhanced T1-weighted imaging (FS) -Subtraction and MIP		

(Heacock et al., 2016)	-Sagittal unenhanced T1-weighted imaging (FS) -Sagittal first contrast-enhanced T1-weighted (FS) -Subtraction -No previous imaging	Abbreviated protocol 1 + With previous imaging	Abbreviated protocol 1 + With previous imaging + T2-weighted imaging (FS)
(Moschetta et al., 2016)	-Axial short T1 inversion recovery (STIR) -Axial T2-weighted imaging turbo-spin-echo (TSE) -3D Unenhanced THRIVE -3D Intermediate contrast-enhanced THRIVE (3 min after gadolinium injection)		
(Pineda et al., 2016)	-Axial pre and post contrast-enhanced T1-weighted (FS) imaging with high spatial and temporal resolution		
(Machida et al., 2017)	-Unenhanced T1-weighted imaging (FS) -First contrast-enhanced T1-weighted imaging (FS)		
(Chen et al., 2017)	-Unenhanced T1-weighted imaging (FS) -First contrast-enhanced T1-weighted imaging (FS) -MIP		
(Strahle et al., 2017)	-Axial T2-weighted imaging Unenhanced T1-weighted imaging (FS) - Axial early contrast-enhanced T1-weighted imaging (FS) -Axial late contrast-enhanced T1-weighted imaging (FS)		
(Petrillo et al., 2017)	-Axial unenhanced T1-weighted imaging (FS) -Axial first contrast-enhanced T1-weighted imaging (FS)		
(Panigrahi et al., 2017)	-Axial unenhanced T1-weighted imaging (FS) -Axial first contrast-enhanced T1-weighted imaging (FS) -Subtraction MIP		
(Romeo et al., 2017)	-Axial unenhanced T1-weighted imaging (FS) -Axial three contrast-enhanced T1-weighted imaging (FS) -Subtractions at 3 time points		

(Oldrini et al., 2017)	MIP	Abbreviated protocol 1 + Contrast-enhanced TRICKS acquisitions at 12 timepoints	Abbreviated protocol 1 + Contrast-enhanced TRICKS acquisitions at 12 timepoints+ Unenhanced T1-weighted imaging (FS)+ T2 weighted imaging
(Choi et al., 2018)	-Sagittal T2-weighted imaging (FS) -Sagittal unenhanced T1-weighted imaging (FS) -Sagittal first contrast-enhanced T1-weighted imaging (FS) -Subtraction and MIP		
(Dogan et al., 2018)	-Axial T2-weighted imaging DIXON -Axial pre and post contrast-enhanced T1 weighted imaging DIXON (FS)		
(Oldrini et al., 2018)	-Sagittal 3D unenhanced T1W-weighted VIBRANT -1st Sagittal 3D contrast-enhanced T1W-weighted VIBRANT -Subtraction		

Key: **THRIVE**- 3D gradient echo sequence (Philips vendor name)
DIXON- fat suppression technique based on chemical shift
VIBRANT-volume image breast assessment (fat sat) (GE vendor name)

(Liney, 2010)

In the studies listed in Table 2.4, the abbreviated protocol generally consisted of an axial unenhanced and first contrast enhanced T1 weighted sequence (Leithner et al., 2019). Some studies opted to study more than one abbreviated protocol as seen in Table 2.4. Subtraction and MIP images are also commonly used in studies such as Choi et al., 2018; Harvey et al., 2016; Kuhl et al., 2014; Mango et al., 2015 and Panigrahi et al., 2017. The MIP and subtraction sequences do not increase the scanning time as they are reconstructed from the T1-weighted images obtained (Deike-Hofmann et al., 2019). In some certain studies (Chen et al., 2017; Heacock et al., 2016; Oldrini et al., 2018 and Romeo et al., 2017) the

researchers opt to use either subtraction or MIP. Some studies included a T2-weighted, STIR and second or third contrast-enhanced T1-weighted sequence (Leithner et al., 2019). Contrast enhancement was used in all the abbreviated protocols indicating its importance in diagnostic accuracy. Current techniques such as diffusion-weighted imaging (DWI) are not sensitive enough to replace contrast enhanced breast MRI completely (Mann et al., 2019b)

2.9 Strengths of an abbreviated breast MRI

2.9.1 Comparable performance indicators

An abbreviated MRI breast protocol takes advantage of the high sensitivity and specificity of breast MRI while benefiting from reduced cost and time (Marshall & Plecha, 2020). To date, many abbreviated breast MRI scans were performed and studied in over 4500 women (Leithner et al., 2018). Sung et al. (2016) diagnosed more invasive cancers with MRI while DCIS was mostly detected by mammography in women at high-risk who performed both MRI and mammography. When using the abbreviated protocol, it was observed that mainly early-stage invasive cancers and predominatly intermediate or high-grade DCIS were detected (Dogan et al., 2018; Harvey et al., 2016; Heacock et al., 2016; Kuhl et al., 2014; Machida et al., 2017; Mango et al., 2015; Oldrini et al., 2018; Panigrahi et al., 2017; Petrillo et al., 2017; Romeo et al., 2017). The studies highlight that using an abbreviated MRI protocol as supplemental screening detects biologically relevant cancers and those which are occult on mammography (Morris, 2014). The ability of MRI to detect more aggressive cancers should impact the mortality and morbidity associated with breast cancer (Pham et al., 2020).

The primary abbreviated protocol set up by Kuhl et al. (2014) consisted of an unenhanced non-fat saturated axial T1- weighted and first contrast-enhanced axial T1-weighted sequence, subtraction imaging, and a single MIP image. The abbreviated MRI

protocol achieved an equal diagnostic accuracy as the full protocol. The findings by Mango et al. (2015) agreed with Kuhl et al. (2014) that using MIP imaging alone is not sufficient to accurately detect breast cancer. Following these two preliminary studies, certain abbreviated protocols included axial T2 weighted or axial STIR sequences while others solely relied on contrast enhanced MRI sequences. Moschetta et al. (2016) used axial STIR, axial T2-weighted sequences, a pre-contrast, and single post contrast T1-weighted axial sequence and found no significant difference in diagnostic accuracy between full and abbreviated protocols. Choi et al. (2018) screened 725 women, 12 malignancies were detected, with 5 lesions visible on the abbreviated MRI protocol alone.

The abbreviated MRI protocol evaluated was made up of fat-suppressed T2 weighted axial sequence, pre- and post contrast T1 weighted axial sequence, and subtracted MIPs (Choi et al., 2018). Dogan et al. (2018) eliminated STIR from the abbreviated protocol and used T2 weighted axial imaging and the axial Dixon sequence for dynamic contrast enhanced (DCE) MRI, which yielded the same image quality equivalent to the full protocol. Petrillo et al. (2017) used one pre-contrast T1 weighted and first post-contrast T1 axial weighted while Romeo et al. (2017) opted for one pre-contrast T1 weighted sequence and three post-contrast axial sequences instead of the first only. Both abbreviated MRI protocols yielded comparable diagnostic accuracies to the full MRI protocol (Petrillo et al., 2017; Romeo et al., 2017). The comparison of the performance indicators in published abbreviated protocols are summarised in Table 2.5.

Table 2.5 Diagnostic Accuracy of Published abbreviated protocols compared to the full MRI protocol

Author	**Setup**	**Sensitivity % (compared to full protocol)**	**Specificity % (compared to full protocol)**	**PPV % (compared to full protocol)**	**NPV % (compared to full protocol)**
(Kuhl et al., 2014)	Screening mild risk/ dense breasts	100 (100)	94.4 (95)	31.4 (33)	100 (100)
(Mango et al., 2015)	Known cancer	96	N/A	N/A	N/A
(Grimm et al., 2015) **Protocol 1 as in Table 2.4**	Selected cases	86 (95)	52 (52)	N/A	N/A
(Grimm et al., 2015) **Protocol 2 as in Table 2.4**	Selected cases	89 (95)	45 (52)	N/A	N/A
(Harvey et al., 2016)	High- risk screening	100 (100)	N/A	N/A	N/A
(Heacock et al., 2016) **Protocol 1 as in Table 2.4**	Known cancer	98	N/A	N/A	N/A
(Heacock et al., 2016) **Protocol 2 as in Table 2.4**	Known cancer	99	N/A	N/A	N/A
(Heacock et al., 2016) **Protocol 3 as in Table 2.4**	Known cancer	99	N/A	N/A	N/A
(Moschetta et al., 2016)	Screening, problem solving, preoperative staging	89 (92)	91 (92)	64 (68)	98 (98)

(Machida et al., 2017) **Observer 1**- 15 years of experience	Consecutive cases	87 (87)	92 (90)	69 (66)	97(97)
(Machida et al., 2017) **Observer 2**- 14 years of experience	Consecutive cases	94 (97)	83 (90)	55 (67)	98 (99)
(Chen et al., 2017)	Screening mild risk/ dense breasts	94 (100)	88 (95)	22 (41)	100 (100)
(Petrillo et al., 2017)	Selected cases	100 (100)	75 (77)	74 (75)	100 (100)
(Panigrahi et al., 2017)	High-risk screening	82 (82)	97 (97)	N/A	N/A
(Romeo et al., 2017)	Consecutive cases	99 (97)	93 (95)	95 (97)	98 (95)
(Oldrini et al., 2017) **Observer 1**	High risk screening, problem solving, preoperative staging, nipple discharge	93 (93)	83 (60)	87 (74)	90 (87)
(Oldrini et al., 2017) **Observer 2**	High risk screening, problem solving, preoperative staging, nipple discharge	93 (93)	71 (58)	79 (73)	89.5 (87.5)
(Choi et al., 2018)	Personal history of breast cancer	100	89	N/A	N/A
(Oldrini et al., 2018)	Staging, high-risk screening, symptomatic cases, lesion characterisation	100(100)	94 (95)	N/A	N/A

2.9.2 Shorter acquisition time

There is no published standardised full breast MRI protocol however, on average this requires 30 to 40 minutes image acquisition to generate several hundred images for interpretation (Ko & Morris, 2019). The first abbreviated protocol produced by Kuhl et al. (2014) had an acquisition time of 3 minutes. Throughout the years a variety of abbreviated protocols were generated with different acquisition times however, none of them had more than 15 minutes of scanning time (Deike-Hofmann et al., 2019). Harvey et al. (2016) and Panigrahi et al. (2017) were the only two studies which managed to reduce the acquisition time to 4 and 3 minutes respectively. Pham et al. (2020) discussed how three abbreviated MRI scans can be completed in the slot allocated for a full MRI scan. The shortened acquisition time may directly lead to reduced motion, discomfort, costs and a more tolerable scan for patients with claustrophobia (Pham et al., 2020). Short acquisition times result in less exposure to the risks associated with MRI such as the exposure to an electromagnetic field in the RF range which can induce biological effects through direct heating (Hartwig et al., 2009). Other than the risk of heating, during magnetic field changes, a loud knocking sound is created which can be harmful, if there is no adequate ear protection (McJury, 2022).

An abbreviated protocol generates less images resulting in a shorter interpretation time, for example Kuhl et al. (2014) reported a 30 second reading time. All the studies performed after Kuhl et al. (2014) managed to generate a short interpretation time unlike Grimm et al. (2015), who had 3 minutes interpretation time for both the full and abbreviated protocol. When compared with the interpretation time of 2 to 4 minutes of mammography, the abbreviated MRI protocol proved to have a faster interpretation time (Haygood et al., 2009).

2.9.3 Decreased cost

Cost has been a long-standing barrier to the application of screening the average population with MRI (Marshall & Plecha, 2020). Apart from the initial cost price of the MRI equipment, the major cause of high costs of breast MRI is due to the long acquisition times (Leithner et al., 2018). The abbreviated protocol was introduced in efforts to reduce the costs associated with scanning time (Kuhl et al., 2014; Marshall & Plecha, 2020; Vinnicombe et al., 2021). The short reading time obtained with the abbreviated protocol counteracts the high costs of the MRI (Kuhl et al., 2014). A simulation developed by Mango et al. (2019) in the United States found that the aggregate cost for MRI screening for 24 years costs $13.02 billion whilst $13.03 billion for mammography screening. Mango et al. (2019) observed that the initial cost of the implementation of a breast MRI screening program is high.

2.10 Challenges associated with the abbreviated breast MRI

2.10.1 Contrast Agents

Currently the backbone of any abbreviated protocol is the contrast-enhanced sequences which provide excellent sensitivity (Leithner et al., 2018). However, concerns about the use and safety of gadolinium-based contrast agents (GBCA) is increasing in the light of new evidence (Pham et al., 2020) which suggests that gadolinium is deposited and retained in the brain, bone, skin and other tissues (Gulani et al., 2017; Ramalho et al., 2016). The controversy surrounding the safety of GBCA has initiated the recommendations to use GBCA only when essential and if a diagnosis cannot be made with unenhanced scans (Dekkers et al., 2018; Gulani et al., 2017). Using contrast-enhanced abbreviated protocols for annual or biannual screening increases the potential for additional gadolinium deposit in the brain (Pham et al., 2020). To date there is no scientific evidence that the retention of gadolinium in the brain has an adverse clinical effect (Leithner et al., 2018; Pham et al., 2020). GBCA have been used for more than 20 years and the evidence suggests that it is safe

to use (Pham et al., 2020). GBCAs have not yet been prohibited however, efforts have been made to develop unenhanced MRI techniques that have an equivalent diagnostic accuracy to breast MRI screening (Leithner et al., 2018).

Diffusion weighted imaging (DWI) has emerged as a valuable and robust technique in studies exploring an alternative for contrast-enhanced MRI (Leithner et al., 2018). DWI is an imaging technique that measures the mobility of water molecules within tissue, based on the differences in Brownian motion (Amornsiripanitch et al., 2019). On DWI breast cancer will have reduced diffusivity and thus appear hyperintense to surrounding tissues (Amornsiripanitch et al., 2019). Several authors have investigated the use of DWI for an unenhanced MRI examination with promising results. Shin et al. (2016) compared an enhanced protocol against an unenhanced protocol made up of DWI and T1-weighted imaging which obtained similar detection rates and diagnostic accuracies. The study by Baltzer et al. (2017) achieved similar results for diagnostic performance when using a DWI protocol against a contrast-enhanced MRI with T2 weighted imaging. Amornsiripanitch et al. (2019) reviewed a variety of studies and concluded that the overall sensitivity is lower in DWI than with dynamic contrast enhanced MRI. However, when studies compared DWI with mammography, DWI had a superior overall sensitivity for cancer detection than mammography. When DWI and mammography were combined the sensitivity improved to 93% rather than 74% and 64% with DWI and mammography alone respectively (Kazama et al., 2012) . Unenhanced DWI alone can be used as a supplemental screening to mammography (Pham et al., 2020). A variety of studies have investigated abbreviated unenhanced protocols with different combinations of T1 or T2 weighted with DWI. In these studies the abbreviated unenhanced MRI obtained an equal or superior sensitivity to mammography (Baltzer et al., 2017; Bickelhaupt et al., 2016; McDonald et al., 2016; Shin et al., 2016).

A limitation of DWI is that sensitivity is limited only in lesions which are smaller than 12mm or presenting with diffuse non mass enhancement (Pinker et al., 2018). The potential of DWI is encouraging however more studies are required with improved protocols and postprocessing techniques (Pham et al., 2020; Leithner et al., 2018).

2.10.2 Lack of standardised protocols

The abbreviated MRI protocol has become widely accepted yet magnetic field strengths and scan protocols are not yet harmonised (Pham et al., 2020). Despite the variability between each abbreviated MRI protocol, diagnostic accuracy and cancer detection rates were equivalent when comparing the full versus abbreviated protocol (Ko & Morris, 2019). Ko and Morris (2019) reviewed a variety of abbreviated protocols investigated throughout the years and in general, the studies used were pre-contrast T1 and first post-contrast T1 with the addition of other options such as subtraction, MIP, second and third points post contrast, T2 weighted images, DWI and STIR images (Ko & Morris, 2019).

Even the two studies performed by Kuhl et al. (2014) and (2017) used two different protocols that were less than 10 minutes duration each. In the first study Kuhl et al. (2014) used axial T1-weighted before and then immediately after contrast injection together with subtracted and MIP images. In the later study performed in 2017 the protocol consisted of axial T1-weighted prior to and four times after contrast injection with the addition of an axial T2-weighted sequence (Kuhl et al., 2017). The addition of the axial T2-weighted sequence resulted in a 37.7% decrease in the number of BI-RADS 3 categories which was changed to BI-RADS 2 (Kuhl et al., 2017). Bickelhaupt et al. (2016) analysed which sequences in a full diagnostic protocol were the most relevant for a confident breast cancer diagnosis. The authors concluded that T2-weighted, T1-weighted pre contrast, and first and late postcontrast images are essential to enable a rapid breast cancer screening. While Heacock et al. (2016)

concluded that T2 weighted provided the most lesion characterisation with the same cancer detection rate.

Currently, at the time of writing this dissertation the ECOG-ACRIN (Eastern Cooperative Oncology Group- American College of Radiology Imaging Network) 1141 (EA1141) trial by Christiane Kuhl is working to compare the abbreviated protocol with DBT for breast cancer screening in women with dense breasts. Once the results of this prospective randomised EA1141 study are released, this may facilitate an agreement on a standard abbreviated MRI protocol.

2.10.3 Potential Decrease in Performance Indicators

MRI was given the reputation as a high-sensitivity, low-specificity imaging modality due to results from earlier studies (Kuhl, 2019). The metric to rate the power with which a health screening method differentiates benign from malignant disease is not specificity but based on the PPV. Early trials produced unsatisfactory PPV values for MRI screening (Kriege et al., 2004; Warner et al., 2004; Leach et al., 2005). MRI then was still a new modality unlike mammography which was well developed (Kuhl et al., 2019). With the improvement of radiologists' expertise in MRI interpretation of breast images and appearance on different sequences, the PPV of MRI for breast cancer screening became equivalent to mammographic screening (Kuhl et al., 2010).

The elimination of certain sequences from the full protocol may potentially affect both the recall rate and limit interpretation of certain breast cancers (Ko & Morris, 2019). The increased use of the abbreviated MRI protocol for screening can increase the risk of potential pitfalls, such as recall rates, increased biopsies, BI-RADS 3 assessment rate, low PPV of biopsies performed (Pham et al., 2020). Indeterminate findings on an abbreviated MRI protocol would require additional diagnostic evaluation to enable characterisation therefore, increasing the overall cost of MRI (Ko & Morris, 2019). The study by Kuhl et al.

(2014) revealed that one-third of BI-RADS category 3 (probably benign) were downgraded to BI-RADS category 2 (benign), eliminating the unnecessary short-term follow up. This finding created the concern that abbreviated MRI protocols may result in an increase in recall rate and decreased specificity (Ko & Morris, 2019; Kwon et al., 2021). Studies on the abbreviated MRI protocol following Kuhl et al. (2014) obtained equivalent sensitivities and specificities for cancer detection indicating the feasibility of an abbreviated protocol (Grimm et al., 2015; Abe et al., 2016; Machida et al., 2017; Mann et al., 2014; Morris, 2014).

To address some of these issues Pham et al. (2020) suggested that radiologists training and the use of guidelines on how to interpret abbreviated MRI protocol findings are required. Radiologists must pass an MRI interpretation test before they read studies, to ensure that a more uniform threshold is used when determining the need to recall patients for an abnormality (Pham et al., 2020). The monitoring of BI-RADS category 3, 4 or 5 rates need to be audited regularly (Pham et al., 2020).

2.10.4 Timing of scan

Existing recommendations suggest that women should have their MRI scan in the second week of the menstrual cycle, for background parenchymal enhancement (BPE) to be the lowest (DeMartini et al., 2012; Ellis, 2009). With a low BPE any abnormalities are more visible and there are less false positive findings (DeMartini et al., 2012; Ellis, 2009; Kuhl et al., 1997). However, later studies have shown that there is no need to scan at certain times during the menstrual cycle (Dontchos et al., 2019; Lee, Bryce, et al., 2020). The study by Lee, Bryce, et al. (2020) evaluated 1536 MRI examinations and concluded that there was no difference in BPE, PPV, cancer detection rate, sensitivity or specificity dependent on the time of the menstrual cycle. However, Dontchos et al. (2019) evaluated 320 MRI examinations and did not find any association between BPE and menstrual cycle. Similarly, to Lee, Bryce et al. (2020) interpretation rate, positive biopsy rate, cancer yield, sensitivity,

and specificity did not differ significantly on the basis of menstrual cycle. Eliminating the need to scan women at certain times in the menstrual cycle would improve access and scheduling of abbreviated MRI for screening (Pham et al., 2020).

2.11 MRI report structure

An MRI report irrespective whether full or abbreviated should be concise and standardised. The ACR BI-RADS Atlas set up a report structure which consists of 7 points that an MRI report should contain (Morris et al., 2013).

1. **Indication for examination**

A brief description for why the examination is being performed and the patient's clinical history. The indications should include the reason for performing breast MRI (screening, follow-up, staging, pre-operative or problem solving), clinical abnormalities, previous biopsies and hormonal status (Morris et al., 2013).

2. **MRI technique**

A detailed description of the technical aspects of the MRI scan should be given prior to the actual report. The types of sequences used in the MRI scan, if contrast was used, any post processing techniques and any titanium markers visualised indicating biopsy of the area (Morris et al., 2013).

3. **Description of overall breast composition**

The breast composition is divided into two: the fibroglandular tissue and the amount of background parenchyma enhancement (BPE) on the MRI. The fibroglandular tissue describes the density of the breast which is divided into four density categories: 1-almost entirely fatty, 2- scattered areas of fibroglandular density, 3-heterogeneously dense and 4-extremely dense (D'Orsi et al., 2013). The BPE is the visually estimated enhancement of the fibroglandular tissue which is divided into four categories based on the level of enhancement: a- minimal, b- mild, c- moderate and d- marked (Morris et al., 2013). If

implants are present, it is important that information regarding their composition is included (Morris et al., 2013).

4. **Clear description of any important findings**

Any abnormal findings in the MRI scan should be described by indicating the location, the lesion type and descriptors (Morris et al., 2013). The descriptors should include size and location of each lesion; right or left breast (quadrant, clock-face position or central, retro areolar and axillary tail) (Morris et al., 2013). Any abnormal enhancement may include the following: artifacts, focus, masses, non-mass enhancement, intramammary lymph node, skin lesion, non-enhancing findings, associated features (e.g., nipple retraction, skin retraction etc…), fat-containing lesions (e.g., lymph nodes), stability of enhancement, kinetic curve assessment and implants (Morris et al., 2013).

5. **Comparison to previous examination(s)**

The current examination should be compared to any previous examinations with the date specified (Morris et al., 2013). Comparison should be made to any examination including MRI, mammography, US and any other relevant imaging modalities (Morris et al., 2013).

6. **Assessment**

The category for assessment is based on the BI-RADS categories developed for mammography. The ACR developed the BI-RADS categories as a standardised format and universal terminology ((D'Orsi et al., 2013; Ghaemian et al., 2021). BI-RADS categories includes seven categories from zero to six, the higher the number indicates the likelihood of malignancy (Ghaemian et al., 2021). The ACR does not only indicate the level of suspicion for cancer but also recommendations for follow-up management (Table 2.6) (Gupta et al., 2017).

Table 2.6 ACR BI-RADS assessment categories (ACR BI-RADS®-Breast MRI, In ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, 2013, American College of Radiology)

BI-RADS score	Assessment	Likelihood of cancer	Management
0	Incomplete	N/A	Recommend additional imaging: mammogram or targeted US
1	Negative	Essentially 0% likehood of malignancy	Routine breast MRI screening if cumulative lifetime risk ≥ 20%
2	Benign	Essentially 0% likehood of malignancy	Routine breast MRI screening if cumulative lifetime risk ≥ 20%
3	Probably benign	≥ 0% but ≤ 2% likehood of malignancy	Short-interval (6-month) follow-up
4	Suspicious	> 2% but < 95% likehood of malignancy	Tissue diagnosis
5	Highly suggestive of malignancy	≥ 95% likehood of malignancy	Tissue diagnosis
6	Known biopsy-proven malignancy	N/A	Surgical excision when clinically appropriate

Categories 1 and 2 indicate that there is no evidence of malignancy (Morris et al., 2013). While categories 3 to 5 indicate a suspicion of malignancy but must be investigated further (Morris et al., 2013). In category 6 a cancer diagnosis has already been established and the lesion is visualised on the MRI for additional evaluation (Morris et al., 2013). In mammography and US, category 4 is subdivided into 4A, 4B and 4C on the basis of likelihood for malignancy: 4A- low suspicion for malignancy (>2%- ≤ 10%), 4B- moderate suspicion for malignancy (>10%- ≤ 50%), 4C- high suspicion for malignancy (>50%- < 95%) (Strigel et al., 2017). However, in breast MRI category 4 is not subdivided due to the shortage of data available to guide practice in MRI (Strigel et al., 2017). The BI-RADS score is commonly used in most of Europe and North America (Taylor et al., 2011). The UK Royal

College of Radiologists Breast Group (RCRBG) and the Australian National Breast Cancer Centre (NBCC) formed a 1 to 5 point scoring system (Table 2.7) (Maxwell et al., 2009).

Table 2.7 Comparison of different classification systems (Maxwell et al., 2009)

Category	BI-RADS	NBCC	RCRBG
0	Assessment incomplete	N/A	N/A
1	**Negative** (Routine screening)	No significant abnormality.	Normal/no significant abnormality.
2	**Benign finding** (Routine screening)	**Benign findings** (No further imaging is required)	**Benign findings**
3	**Probably benign finding** (Short interval follow up)	**Indeterminate/equivocal findings** (Requires further investigation (biopsy))	**Indeterminate/probably benign findings** (Further investigation is indicated)
4	**Suspicious abnormality** (Tissue diagnosis-biopsy)	**Suspicious findings of malignancy** (Requires further investigation. May require excisional biopsy)	**Findings suspicious of malignancy.** (Further investigation is indicated)
5	**Highly suspicious of malignancy** (tissue diagnosis-biopsy)	**Malignant findings.** Requires further investigation, even if non-excision (percutaneous) sampling is benign	**Findings highly suspicious of malignancy.** (Further investigation is indicated)
6	**Known biopsy-proven malignancy**	N/A	N/A

7. **Management**

Management is the description of what should be done for each BI-RADS score (Table 2.7). If a suspicious lesion of category 4 or 5 is detected then it warrants a tissue diagnosis (biopsy) to confirm the presence of malignancy (Morris et al., 2013).

2.12 Conclusion

In this chapter the current literature available was analysed and an overview related to the abbreviated breast MRI was provided. The literature indicates a growing interest in using MRI for breast cancer screening and various studies have assessed the quality of the abbreviated protocol. There is ample evidence that MRI has a superior diagnostic accuracy and outperforms mammography or US as an imaging tool for breast cancer. However, important issues need to be addressed if the abbreviated protocol is to be used routinely for breast cancer screening. Throughout the literature there is a lack of standardisation surrounding the abbreviated protocol which introduces certain uncertainties. In the next chapter, the methodology used to carry out this study is discussed.

Chapter 3

Research Methodology

3.1 Introduction

The following chapter presents and discusses the methodological design adopted in this research study, to achieve the research aim and objectives as presented in chapter one. The rationale behind the research approach used in this study is provided and a detailed evaluation of the selection of research participants, sampling methodology, data collection procedures and data analysis will be conveyed.

3.2 Research Design

Research is conducted by the systematic collection, interpretation and evaluation of data in accordance with established methodologies (Ozhan Caparlar & Donmez, 2016). A research design "*is a blueprint to guide the research process*" (Abutabenjeh & Jaradat, 2018, p.2) from the research question to the end result. The research design aids to collect and analyse data to improve the understanding of the selected topic (Abutabenjeh & Jaradat, 2018).

A quantitative, retrospective, and comparative non-experimental methodology was deemed an appropriate research design for this study.

3.2.1 Quantitative Approach

As defined by Polit and Beck (2017), quantitative research is "*the investigation of an occurrence that leads to the exact measurement and quantification involving a controlled design*" (p.741). Quantitative studies are used to establish the relationship or trends between certain variables (Dellis et al., 2014). Quantitative research as described by Watson (2015) as a way of thinking about the world where measurements are made, analysis is applied, and conclusions are drawn. The data gathered from quantitative research is numerical data which may be measured in units or placed into categories (Mcleod, 2017). Quantitative research is typically performed in a systematic fashion from the definition of a problem to a solution

(Polit and Beck, 2017). The numerical data was collected from the images being evaluated and was statistically analysed with a quantitative approach.

3.2.2 Retrospective Study

The timing of the research in terms of the outcome determines if the study is classified as prospective or retrospective (Ranganathan & Aggarwal, 2018). A prospective study attempts to establish the outcome of an event or what is most likely to happen (Gerrish & Lacey, 2010). In a retrospective study, the outcome of interest has already occurred, and the data would already be present prior to the study (Polit & Beck, 2017). In a study with a retrospective design, the researcher attempts to determine the factors that have caused an outcome in the present (Polit & Beck, 2017). When doing a retrospective study, the researcher relies on the already available data which was not intended for research purposes, while in a prospective study the desired data is guaranteed to be included (Gerrish & Lacey, 2010).

Locally, breast MRIs using the full protocol are currently being performed for symptomatic patients who require further imaging, after having a negative mammogram and/or ultrasound, in the follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer and for patients who have breast implants to check for any ruptures. Due to the small number (approx. 150) of breast MRIs performed locally annually, a retrospective approach was deemed as being the most appropriate design for this study to obtain the stored data over the years and therefore obtain a large enough sample size to attempt generalisation of findings. However, a prospective design was used in the second phase of the study where the radiologists analysed the abbreviated protocol and filled in the data collection tool.

3.2.3 Comparative Study

The research design for this quantitative research approach was a comparative, non-experimental approach. A comparative approach attempts to identify any relationship between two or more groups (Grove & Gray, 2019). The relationship under investigation would be whether there is a relationship between using an abbreviated protocol vs. use of the full protocol on the diagnostic accuracy of the images obtained from patients who performed a breast MRI with either a normal or abnormal finding. In a comparative approach, the researcher would not manipulate any variables, but will only investigate the effects which in this case is the diagnostic accuracy. Both protocols were compared to identify if the abbreviated protocol may be of benefit in the screening environment. The abbreviated protocol was extracted from the full protocol and used separately. This study was performed to examine if the diagnostic accuracy persisted with an abbreviated protocol, then the comparative approach was ideal to achieve the aims of the research question.

3.2.4 Non-experimental Study

A non-experimental approach was adopted by the researcher since there was no manipulation of the variables, but the variables were examined as they naturally occurred in the environment, without implementing any changes to the data (Grove & Gray, 2019). As described by Polit and Beck (2018), the researchers in a non-experimental study are bystanders as they collect quantitative data without introducing any treatments. Unlike in an experimental study, no control group and experimental group were included in this study and there was no attempt by the researcher to manipulate the independent variable thus, the research was considered to be a non-experimental research design (Polit & Beck, 2018).

3.3 Overview of methodology

An image data set was compiled from MRI breast examinations performed on patients performed between January 2019 to December 2021. MRI breast examinations of

patients who fulfilled the inclusion and exclusion criteria listed in Section 3.3.2.1 were selected to form part of the image data set. Any data related to the patient was collected by an intermediary person, a radiographer working in the MRI unit, on behalf of the researcher. The intermediary person contacted the patients and provided the required information about the study and whether they gave their permission for their images and clinical data to be used as part of the image data set for the study. Once the intermediary person received consent from the patients, the sequences making part of the abbreviated protocol were extracted from the full protocol. The histopathological results and previous imaging results were also collected by the intermediary person to use as the gold standard. The intermediary person made sure that the case was anonymised and that each case was assigned a number. The radiologists would access the images from their respective workstation via the Picture Archiving and Communication System (PACS) by entering the case number assigned by the intermediary person. The radiologist would be blinded to any other patient history, only the abbreviated protocol would be available for the radiologist to view.

For each set of images, the radiologist filled in the final BI-RADS score in the data collection tool. A **negative** abbreviated MRI examination was classified as BI-RADS 1 or 2 while a **positive** abbreviated MRI examination was classified by a BI-RADS 3, 4 or 5. The findings from the radiologists would then be compared to the gold standard for each case. Taking BI-RADS ≥3 as the optimal classification criteria, the sensitivity, specificity, PPV and NPV of the abbreviated protocol were then calculated. The sensitivity, specificity, PPV and NPV were calculated based on the formulas described in Section 2.7.

3.3.1 Target and Accessible population

The target population, accessible population, sampling criteria and sample technique should be formulated prior to the start of the study (Polit & Beck, 2017). The target population refers to the total population that the researcher is interested in studying (Polit &

Beck, 2018). Grove and Gray (2019) defined the target population as participants who meet the sampling criteria. The researcher would generalise the study results to the target population (Gerrish & Lacey, 2010). The accessible population consisted of participants from the total population who were accessible to the researcher (Polit & Beck, 2018).

Patient Participants:

The target population in this study were patients who performed a breast MRI examination in Malta. In this regard, the accessible population included patients who performed a breast MRI at the medical imaging department of a public general hospital in Malta between January 2019 and December 2021. The period was conveniently selected to have a larger accessible population from which the sample was selected.

Radiologist participants:

Both the target and accessible population included all breast consultant radiologists in the public general hospital in Malta.

The sampling criteria and sampling methods used are discussed in Sections 3.3.2 and 3.3.3

3.3.2 Sampling Criteria

Sampling criteria comprise of setting up characteristics to obtain a uniform population of a study (Polit & Beck, 2010). Gray, Grove and Sutherland (2017) stated that the sampling criteria selected determines the target population and "*the sample is selected from the accessible population within the target population*" (p.619). If a study has a representative sample, the findings, once the study is complete, could be generalised from the sample to the target population (Gray et al., 2017).

3.3.2.1 Inclusion and Exclusion Criteria

Inclusion criteria are characteristics that the subject must possess to participate in the study (Grove & Gray, 2019). While exclusion criteria are characteristics that can cause the subject to be excluded from the population even if all the inclusion criteria are met (Grove & Gray, 2019). Exclusion criteria are essential to ensure that the sample does not contain any undesirable characteristics that should not be included (Polit & Beck, 2018).

Patient participants:

For the purpose of this study, the following inclusion criteria were set:

- Patients who were scanned using the 3.0-T (Tesla) MRI Philips Ingenia with a dedicated prone breast coil (7 channel coil), this to maintain reproducibility of image quality.
- Patient scanned with the same full protocol had to be used for the selected cases.
- Patients must have histo-pathological findings from a biopsy or availability of a 12-month of negative findings on follow-up imaging with either mammography, US or MRI in the absence of a biopsy. The findings represent the true disease status referred to as the '*gold standard'* which was compared to the findings from the MRI report.
- Patients with a pathological finding of breast lobular carcinoma.

The exclusion criteria were:

- Patients who have breast implants or previous breast operations, such as mastectomy or wide local excision since there will be distortion of breast tissue. It is essential that the breast tissue is visible and not obscured as this will influence the findings of radiologists.
- Patients who were uncooperative during the scan and have either stopped the scan or constantly moved resulting in poor quality images.

- Other breast cancers which are not lobular carcinoma were not included in the study to satisfy uniformity.

Radiologist participants:

The inclusion criteria for radiologists were that they are specialised in breast imaging with a minimum of two years of experience in MRI breast reporting. The selected sample of radiologists was based on their availability and willingness to participate.

3.3.3 Sampling Method

Sampling is the term that describes a portion of the population to represent the whole target population being studied (Polit & Beck, 2018). In research there are two basic sampling methods: probability and non-probability sampling schemes. The difference between probability and non-probability sampling is mainly whether the sample was selected at random or not (Trochim, Donnelly & Arora, 2016). Gerrish and Lacey (2010) stated that probability schemes are generally used for quantitative research studies, since any bias or errors may be calculated and accounted for. Probability schemes allow for better generalisation to the target population than non-probability schemes (Gerrish & Lacey, 2010). In probability sampling, the population has an equal opportunity to be included in the sample (Polit & Beck, 2018). Non-probability sampling is used when the population cannot be identified in advance from which the sample can be obtained (Gerrish & Lacey, 2010). In this study two sampling methods were used; consecutive sampling was used for the selection of the participants to use their MR images while radiologists were chosen using convenience sampling.

Consecutive sampling is a type of non-probability sampling, where all the members in the accessible population for a specific period who fit the exclusion and inclusion criteria are selected (Polit & Beck, 2018). Consecutive sampling is the best at controlling any sample bias since all the population available is used (Thewes et al., 2018).

Convenience sampling was used to select radiologists. Convenience sampling is a non-probability sampling method. Participants were selected based on their availability and accessibility (Elfil & Negida, 2017). Convenience sampling was described by Polit and Beck (2018) as the weakest form of sampling, however this is a common sampling method used especially when resources are limited. All radiologists from the population were invited to participate in the study however those who accepted were recruited in the study. In total there were four radiologists within the accessible population, and two accepted to participate in the study.

3.3.3.1 Sampling Size

In quantitative research, sample size is a major concern. Larger sample sizes are better than smaller (Polit & Beck, 2018). Studies with a larger sample size will produce results which better represent the whole population (Polit & Beck, 2018). In comparison studies, the sample size will determine if a statistical significant difference is present between groups (Grove & Gray, 2019). The sample size was limited to 35 patients who satisfied inclusion and exclusion criteria. Since an MRI examination contains several sequences with each sequence having a vast number of images, having a large sample would result in the evaluation process being too long. Acknowledging the researcher's time together with the radiologist's availability, 35 patients were deemed as an adequate amount to satisfy practicality. In the period between January 2019-December 2021 a total of 495 MRI breast scans were performed in the local hospital however, this amount reduced significantly because of the inclusion and exclusion criteria.

Consultation with an experienced statistician was sought to determine an adequate sample size with the limitations presented (L. Pace, personal communication, May 18th, 2022). The programme G*power version 3.1.9.4 was used to determine the adequate sample size to be used in the study. The independent t-test was used to determine the statistical

power based on the sample size of each group. A statistical power of 80% or higher is adequate to determine the effects of the research study (Shreffler & Huecker, 2022). The statistical power is critical to decide the sample size especially when the sample is low (Shreffler & Huecker, 2022). A sample size of 15 for the normal group and a sample size of 20 for the abnormal group provided a statistical power of 81.1% which was considered satisfactory to determine if a statistically significant difference is present between the two groups.

3.4 Data Collection Tool

Data collection commenced after carrying out a review of the available literature and choosing the adequate research design for the study. As suggested by Johnson & Christenses (2012) the method of data collection was selected to attain the appropriate research data from the subjects. Regardless of the type of data collected, the data collection tools are structured to collect and analyse data. Quantitative data tend to be quantifiable and structured to obtain the same information from the subjects in a comparable way (Grove et al, 2013). Unless a data collection tool is available already, then the researcher must create one. As none were available or could be identified for this research study, a self-designed data collection tool was used.

The data collection tool was divided into two sections, the first one was filled in by the intermediary person who recorded the findings of the original MRI report using the full protocol, histo-pathological results or follow up imaging and the other one was completed by the radiologists after reviewing the abbreviated protocol. A copy of the data collection tool may be found in Appendix B. Only the abbreviated protocol was presented to the radiologists, who were blinded to the original report, clinical history, other imaging modality reports and the number of negative and positive cases in the study. The images were made up from a random batch of normal breast MRI scans (n=15) combined with scans which

demonstrated breast lobular carcinoma (n=20) which was confirmed through histo-pathology.

In the data collection tool, the first question asked the radiologists if there was a lesion present in the breast, if yes, then more information was sought regarding the size, location (left/right/both breasts), quadrant, number of lesions, size and if there were any lymph node involvement. Ultimately for each case the radiologist filled in the final BI-RADS score. BI-RADS provide a standardised method of image reporting and reduce confusion by providing a common language among radiologists which enable consistent communications regarding findings and management recommendations (Lee, 2017). The findings presented by the radiologists were compared with the findings obtained from the full protocol MRI report, histo-pathological findings and follow-up imaging.

3.4.1 Validity and Reliability of the Tool

The data collection tool was self-designed by the researcher, therefore both reliability and validity testing were performed prior to the use of the tool in the research study. As stated by Polit and Beck (2018) "*researchers want their inferences to correspond to the truth*" (p.121), hence validity and reliability tests are crucial to obtain results which are significant and credible.

3.4.1.1 Validity Testing

Validity is when the research tool used to collect the data is evaluated to confirm that the tool measures what is intended (Polit and Beck 2018) without bias or misrepresentation (Gerrish and Lacey, 2010). Validity will vary from one sample to another therefore, validity is done to evaluate the tool for a group or purpose, instead of the tool alone (Grove & Gray, 2019). Validity testing is creating an evidence-based argument on how accurately the tool gives the results intended (Gray et al., 2017).

The data collection tool for this study was self-designed since there was no data collection tool available within the local clinical scenario and in the literature available. There are different types of validity which may be considered the main being, content, construct and criterion validity (Grove & Gray, 2019). Content validity was the type of validity assessment chosen for this study as this tests if the research tool being used is easy to understand and whether it correctly reflects what it is anticipated to measure (Grove & Gray, 2019). Content validity was performed by handing out the data collection tool to 'experts' in the field to rate the relevance of the tool (Polit & Beck, 2018). The data collection tool used in the study was validated by two expert radiologists who are specialised in breast imaging with more than 15 years of experience and perform breast biopsies or localisations under image guidance. To measure the content validity index (CVI), the experts were asked to rate how relevant and how clear each item on the data collection tool was in relation to the aims and objectives of the study. The rating scale from Waltz, Strickland and Lenz (2010) was utilised for this purpose.

The experts had to rate every item being recorded according to the 4-point Likert scale, with a rating of 1 indicating that the question was not relevant and a rating of 4 indicating that the statement was very relevant and clear (Waltz, Strickland and Lenz, 2010). Ratings of 1 and 2 were "*content invalid*" while ratings of 3 and 4 were taken to be "*content valid*" (Waltz, Strickland and Lenz, 2010). To calculate the CVI, the items that were rated 3 or 4 were summed up and the total divided by the number of elements rated. A CVI value of 0.9 or more provides evidence of good content validity (Polit & Beck, 2018). Since all items were considered as relevant (rated 3 or 4) the CVI for this study was found to be 1 deeming the research tool to be valid (Zamanzadeh et al., 2015). Once validity testing was performed, a pilot study was conducted and is discussed in Section 3.4.2.

3.4.1.2 Reliability Testing

Validity and reliability are interlinked factors, data cannot be valid if it is not reliable (Cormack, Gerrish & Lathleean, 2015). Reliability concentrates on the consistency of a measurement method (Grove & Gray, 2019). Polit and Beck (2018) described reliability as "*the accuracy and consistency of information obtained in a study*" (p.121). For a data collection tool to be reliable, the same readings should be generated for repeated measures (Gerrish & Lacey, 2010).

Reliability evaluation of radiologists in image quality evaluation

Radiologists who evaluated the images were tested for reliability by means of intra- and inter- rater methods. Inter-rater reliability is a score of how much linearity there is in the results given by different raters (Polit and Beck, 2020). While intra-rater reliability can be described as the degree of agreement among repeats of a diagnostic test performed by a single rater (Polit and Beck, 2020). In the image dataset of the clinical study, duplicate MR examinations were added and presented to each radiologist to facilitate intra-rater reliability testing. The radiologists had no knowledge that some of the examinations were duplicated. Inter-rater reliability was tested by comparing the scores obtained in the data collection tool between the radiologists. The Cohen's Kappa test is applied on variables that present a nominal scale while, the intraclass correlation coefficient (ICC) was used for the BI-RADS score.

Cohen's kappa coefficient is a technique which is used to measure the percentage agreement between the two sets of responses (McHugh, 2012). The kappa (κ) coefficient represents the proportion of the possible agreement. Kappa (κ) values increasingly greater that 0 represent increasing better-than-chance agreement, to a maximum value of +1, which indicates perfect agreement (Artstein and Poesio, 2008). The null hypothesis states that the agreement

between the raters is no different than chance agreement. The alternative hypothesis stated that if the kappa is different from zero there is agreement. If the p-value is < 0.05, the result is statistically significant, and the alternative hypothesis is accepted.

Intraclass correlation coefficient (ICC) is a statistical test that is used to assess the reliability of a tool (Polit & Beck, 2018). ICC is used commonly in test re-test, intra-rater and inter-rater reliability analysis (Koo & Li, 2016). ICC is a number with a value between 0 to 1 (Liljequist et al., 2019), where 0 indicates no reliability while 1 represents perfect reliability with no error. ICC values above 0.8 or 0.9 are regarded as excellent reliability however whether an ICC number is good enough depends on the method being used (Liljequist et al., 2019). The null hypothesis states that if the ICC is 0 no agreement is present. The alternative hypothesis stated that if the ICC is more than zero, agreement is present. Furthermore, a p-value which > 0.05 indicates that the null hypothesis should be accepted and deems the person collecting the data as unreliable. If the p-value is < 0.05 this indicates that the person is reliable.

For both intra-rater and inter-rater reliability only the reliabilty for the variables '*is there a lesion present*' and '*is there lymph node involvement'* could be calculated due to the fact that when the radiologist responded no in statement '*is there a lesion present*' then no other information of the data tool had to be filled in therefore reliability could not be calculated for the other statements.

Intra-rater reliability of each radiologist

Cohen's Kappa test was run to determine if there was agreement between the readings of the radiologists for the variables '*is there a lesion present*' and '*is there lymph node involvement'*. The test revealed satisfactory results as the statistical values were all

<0.05 which indicates agreement between the repeated images for these statements (Appendix C). The BI-RADS score was assessed using the ICC score which produced p values of 0.021 and 0.0001 for radiologist 1 and 2 respectively indicating statistically significant agreement between the two readings for both radiologists (Appendix C).

Inter-rater reliability of each radiologist

Cohen's Kappa test was run to determine if there was agreement between the readings of the first and second radiologists for the variables '*is there a lesion present*' and '*is there lymph node involvement'*. The test revealed satisfactory results as the statistical values were all < 0.05 which indicates good significant inter-rater reliability (Appendix C). The BI-RADS score was assessed using the ICC score which produced p values of 0.086 and 0.0001 for the first and second reading respectively. Unlike the first readings for the final BI-RADS score, the second readings by radiologists 1 and 2 seem to be much more reliable. In the first readings, the BI-RADS score by radiologist 1 was much lower than that of radiologist 2, which led to a low reliability. On the other hand, the second readings resulted to be more comparable and resulted to have a very good reliability as the p value was < 0.05 (Appendix C).

3.4.2 Pilot Study

A pilot study is a small-scale study performed before embarking on the actual research study (Polit and Beck 2018). The pilot study is a trial run of the actual study, which uses the same process, population, intervention, data collection and analysis that will be used in the actual study (Gray et al, 2017). Researchers conduct the pilot study to make any necessary amendments and refine the study sampling process, intervention or measurement of variables (Grove & Gray, 2019).

The pilot study was performed for the image evaluation process. The two radiologists who report breast MRI examinations and considered as experts in the area, and who performed the validity and reliability, also performed the pilot study. The pilot study was a smaller version of the actual study, it was conducted for only four cases. The two radiologists who took part in the pilot study were not included in the actual study. Following the image evaluation process, they were asked if any difficulties were encountered when viewing the images or when filling in the data collection tool. No issues were encountered during the pilot study. However, it was suggested that the data collection period of the actual study should be increased. The reviewers noted that the data collection period coincided with breast awareness month therefore radiologists had an increased workload and for this reason the data collection period had to be extended to last approximately three months. The data collection was performed between September to November 2022.

3.5 Data Collection

Data collection is the systematic gathering of information which is relevant to the research, to reach the aims and objectives of the study (Polit & Beck, 2018). As described by Gerrish and Lacey (2010) the stage of data collection is the most rewarding stage of the research. The data collection could be carried out after ensuring that the tool was valid. The images used in the data collection process were from patients who fulfilled the eligibility criteria and consented to have their images and histo-pathological results accessed by the intermediary person for research purposes. Since this study was performed retrospectively, the patients were already scanned during the period between January 2019 and December 2021 using the full protocol. The patients did not have to be re-scanned to obtain the abbreviated protocol; however the sequences required for the abbreviated protocol were extracted from the full protocol.

The abbreviated protocol selected was based on the literature findings presented in Section 2.8.1 in Chapter 2. The full protocol used locally was described by a radiologist as "*long and unnecessary*" (Personal communication, 22nd November 2021) therefore the abbreviated protocol selected is much shorter and refined as observed in Table 3.1 below. As shown in Table 3.1 the total scanning time was reduced from 32 minutes 15 seconds for the full protocol to 3 minutes 54 seconds for the proposed abbreviated protocol. There was a reduction in scanning time of 29 minutes and 1 second.

Table 3.1 Local full protocol against proposed abbreviated protocol sequences

Local Full Protocol sequences	**Sequence time**	**Proposed Abbreviated Protocol sequences**	**Sequence time**
T1- Weighted -TSE Axial	5.41 min	/	
T2- Weighted- SPAIR Axial	6.10min	/	
Unenhanced Axial Dynamic THRIVE (T1-Weighted) (FS) + **Six** contrast axial enhanced Dynamic THRIVE (T1 Weighted) (FS)	1.18 min each dynamic scan **9.14 min (total)**	Unenhanced Axial Dynamic THRIVE (T1-Weighted) (FS) + **First and second** contrast axial enhanced (early arterial phase) Dynamic THRIVE (T1-Weighted) (FS)	1.18 min each dynamic scan **3.54 min (total)**
eTHRIVE High resolution Sagittal	4.21 min	/	/
T2- Weighted Longer TE higher resolution Axial	4.02 min	/	/
Diffusion Weighted Imaging (DWI)	3.27	/	/
Maximum Intensity Projection (MIP)	0 min	Maximum Intensity Projection (MIP)	0 min
Subtraction Imaging	0 min	Subtraction Imaging	0 min
	Total: **32.15 min**		**Total:** **3.54 min**

The most common abbreviated protocol made use of unenhanced and first contrast-enhanced fat sat T1 weighted axial sequence. Kuhl et al. (2014) made use of the same sequences however, without fat saturation, which differed from all the succeeding abbreviated protocols performed to date. The importance of using the early arterial phase following contrast injection is to detect any potential malignant lesions or rule out the presence of cancer (Petrillo et al., 2017). The MIP of subtracted images provides information regarding non-physiological enhancement while the rest of the abbreviated protocol provides further information on any lesions present (Petrillo et al., 2017).

Out of 17 studies, 7 studies opted not to use the MIP and subtraction imaging as presented in Table 2.4 in Chapter 2 (Dogan et al., 2018; Grimm et al., 2015; Machida et al., 2017; Moschetta et al., 2016; Petrillo et al., 2017; Pineda et al., 2016; Strahle et al., 2017). The MIP and subtraction imaging are generated from post-processing which provide added information to the radiologists without added scanning time.

The intermediary person extracted the sequences for the abbreviated protocol from PACS, anonymised and gave a specific case number to each individual case. Prior to the image evaluation process the intermediary person asked each radiologist taking part to read and sign the consent form. The data collection tool was supplied and explained briefly to the radiologist. The anonymised set of images was presented to the two radiologists taking part in the image evaluation by the intermediary person. The data set consisted of only the abbreviated MRI protocol for 35 patients, with 10 abbreviated protocols repeated for reliability, giving a total of 45 exams for evaluation (Table 3.2). During the image evaluation process, the images were randomly presented to each radiologist. For each set the radiologist had to complete the data collection tool supplied.

Table 3.2 Contents of image data set

Image data set (total of 45 cases)
15 normal findings
20 abnormal findings
10 repeated cases (5 normal and 5 abnormal) for reliability

The display monitors that were used to view the MRI images had a 1280 x1024 (pixels) resolution with a maximum luminance of 200cd/m^2. Digital images must be viewed in low lighting for adequate interpretation. The ambient lighting in the viewing rooms measured at 100cm from a switched off monitor should be between 25-75 lux as set by the American Association of Physicists in Medicine (report 270, 2019). A Physikalisch Technische Werkstatten CD LUX metre model L991263 was used to measure the ambient illuminance which resulted in 39 Lux which was within the recommended range.

The results from both the full and abbreviated MRI scan had to be compared to the true disease status which is generally referred to as the 'gold standard' which is follow up, surgical verification, such as biopsy (Zou et al., 2007). Zou et al. (2007) suggested that the full and abbreviated MRI scans are compared with the 'gold standard' to confirm the findings of the MRI and avoid any verification bias or measurement error.

3.6 Data Analysis

As stated by Grove and Gray (2019) data analysis involves the organisation of data together with the analysis of the data to produce the study results from which conclusions may be drawn. Gerrish and Lacey (2010) stated that the data analysis phase is the most crucial part of the research study. Data analysis was performed by conducting statistical tests to analyse the information collected (Polit & Beck, 2018). Statistical analyses were used to examine and give meaning to the numerical data collected in the study. To analyse the data,

the Statistical l Package for Social Sciences Software (SPSS) version 24 was utilised by the researcher. A statistician was also consulted for assistance.

Receiver Operator Characteristic (ROC) analysis was used to analyse the data. ROC is a valuable tool to evaluate the performance of diagnostic tests (Zou et al., 2007). ROC analysis quantifies how accurately a diagnostic test can differentiate between two patient states '*diseased*' and '*non-diseased*' (Hajian-Tilaki, 2013). ROC analysis functions as a simple graphical tool to display the accuracy of a diagnostic test (Zou et al., 2007). A ROC curve has sensitivity (true positive) plotted on the y-axis against specificity (false positive) on the x-axis across cut-offs which generate the ROC curve (Hajian-Tilaki, 2013). As shown in figure 3.1, test B has a greater discriminate capacity than test A, since it is located closer to the upper left-hand corner (Hajian-Tilaki, 2013). In this study the tests would represent the abbreviated and full protocols. The area under the curve (AUC) of a ROC graph is a measure which averages diagnostic accuracy across the test value spectrum (Hajian-Tilaki, 2013). The AUC is a summary of measured accuracy, which determines the ability of a test to distinguish between diseased and non-diseased (Kumar & Indrayan, 2011). The AUC provides a combined measure of sensitivity and specificity which portrays the inherent validity of diagnostic tests (Hajian-Tilaki, 2013).

The minimum AUC of 0.5 is considered a chance level which is represented by the yellow line in figure 3.1 (Hajian-Tilaki, 2013). The maximum AUC value of 1 means that the diagnostic test is perfect to distinguish between a negative (non-diseased) and positive (diseased) case therefore, the higher the AUC, the better the test is at distinguishing between positive and negative cases (Hajian-Tilaki, 2013). An AUC of 0 suggests that the test is incorrect, and the positive cases are classified as negative and vice versa however, this rarely occurs in clinical practice (Hajian-Tilaki, 2013). An AUC of 0.5 indicates that the diagnostic

test has no ability to distinguish between patients with and without the disease (Mandrekar, 2010). However, the values between 0.5 and 1 have different interpretations (Table 3.3)

Table 3.3 Interpretation of the range of values for AUC between 0.5 and 1 (Mandrekar, 2010)

AUC Value	Interpretation
0.5	No discrimination
0.5-0.7	Poor
0.7 to 0.8	Acceptable
0.8 to 0.9	Excellent
More than 0.9	Outstanding

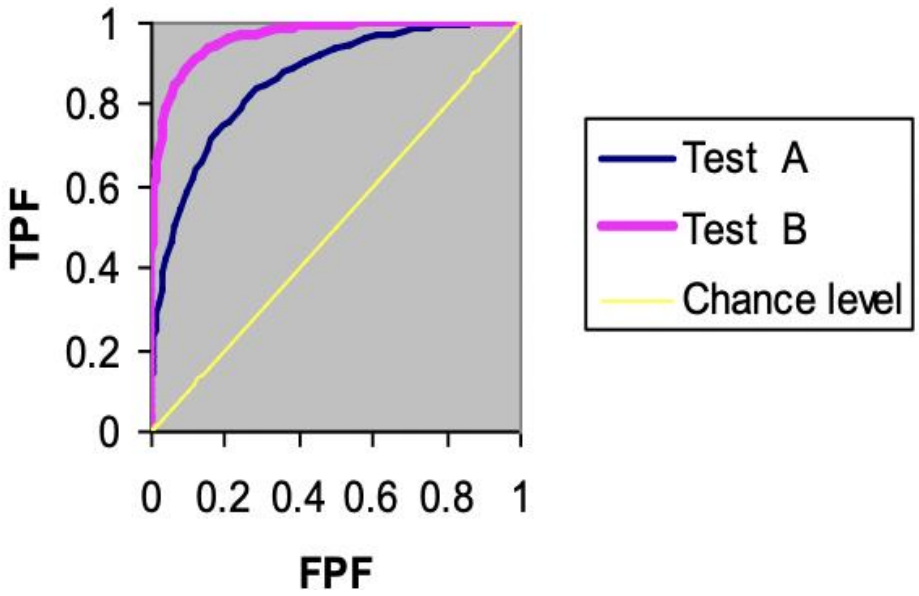


Figure 3.1 An example of an ROC curve (Hajian-Tilaki, 2013)

3.7 Ethical considerations

Ethical considerations must be addressed in any research which involves human participants (Polit & Beck, 2018). Ethical concerns are particularly prominent in healthcare because the line between the expected practice and the collection of data can get blurred (Polit & Beck, 2018). There are three primary ethical principles articulated by the Belmont Report, namely beneficence, respect for human dignity and justice which need to be observed prior to carrying out a research study (Biomedical & Research, 1978).

Prior to embarking on the research process, Ethical permission was sought and obtained from Faculty Research Ethics Committee (FREC) and University Research Ethics Committee (UREC) (FHS-2021-00038). Permission was also sought and obtained from the public general hospital's Chief Executive Officer (CEO). As a requirement to obtain ethical permission, consent from the data protection officer of the hospital was acquired to access the Radiological Information System (RIS) and the PACS to obtain the participants' MRI images from the hospital's database systems. Further consent was obtained from the Chairperson and Radiography Lead of the Medical Imaging Department. All the permissions are attached in appendix A1.

Permission was sought and obtained from three radiographers to act as intermediary persons to retrieve and gather the required data. The roles of the intermediary persons were as follows:

- Access PACS and RIS to obtain the data required to generate the image data set for the radiologists to evaluate,
- Obtain the histo-pathological reports for breast biopsies to be used as the gold standard,
- Invite participants and radiologists to take part in the study and distribute the information sheet and consent forms,
- Retrieve the images from PACS and create the coded anonymised image data set,
- Explain the data collection procedure and obtain the results from the radiologists.

Due to ethical considerations regarding the General Data Protection Regulation (GDPR) of the participants, all eligible patients were contacted through a letter sent by the assigned intermediary persons. Prior to starting the data collection, the patients had to consent to have their images and histo-pathological results used for the sole purpose of this study. Letters

were sent on behalf of the researcher by the intermediary persons to each patient with a self-addressed envelope, if the patients consented to the use of their data the sheet was to be signed and sent back in the self-addressed envelope. Through an information letter given to them by the intermediary persons, the participants were informed that termination of consent was possible at any stage of the study and that withdrawing from the study does not have any effect on the services received from the hospital. All the information was written down both in the information sheet and consent form they received by post. In the study four participants did not send the signed consent form in the self-addressed envelope therefore, it was considered that the patient did not consent to have their information accessed and thus excluded from the study.

To maintain ethical considerations the following was observed:

- The data collected was treated with strict confidentiality and any information gathered was kept under lock and key,
- Images used were anonymised by the intermediary person and the participants could not be identified, no personal data was collected to further ensure patient confidentiality,
- The information letter and consent forms were written both in English and Maltese (Appendix A4), to ensure that the participants fully understood the research study,
- The participants did not have to participate directly. The participants had every right to decide to not participate as participation was voluntary

The researcher must honour all agreements that were made with the participants prior to the study and respect their beliefs throughout the study (Polit & Beck, 2018).

3.8 Limitations and Strengths of the study

Limitations are challenges that arise in a research study which may decrease the generalisability of the findings (Gray et al., 2017). Identifying study limitations is essential and the researcher must acknowledge how these were addressed and how these might have influenced the study findings (Gray et al., 2017). The researcher recognised the limitations and made the effort to try and minimise such limitations throughout the study however, some limitations were beyond the control of the researcher.

The main limitation of the study was the sample size. A small sample size may fail to show a difference between groups if present, not because it is non-existent, but because of the small sample size (Polit & Beck, 2018). There was a limited number of breast MRIs included in the study however, the power sample obtained was still more than 80%.

Another limitation was the availability of normal MRIs, as at the hospital where the study took place a breast MRI is usually performed for patients who are symptomatic or suspicious of malignancy, have been diagnosed with breast cancer following a mammography examination or as follow up of previous breast cancer diagnosis. The radiologists were aware of this and therefore their evaluation could have been biased.

MRI for high-risk patients as a screening tool is not yet available locally and the population sample did not represent the high-risk group but represented only cases of lobular carcinomas as other types of breast carcinomas were excluded. Patients with lobular carcinoma may not necessarily have a similar age profile to patients invited for breast screening. Thus, the sample did not represent patients invited for breast cancer screening.

The images were anonymised by the intermediary person, and the radiologists had no access to any previous imaging or histopathological results. Some of the reports for the full MRI scans, were previously done by the same radiologists who took part in the study,

thus there could have been an element of bias in the study by the radiologists remembering the case. Also, the fact that the radiologists had different years of experience could have had an impact on the results.

Another limitation in this research study is that it had a retrospective design. Therefore, the researcher had to rely on the data available which was not primarily for research purposes The researcher had no other option than to perform the study retrospectively to gather a larger sample size due to the time restriction.

A strength of the research study is that the radiologists were blinded to the clinical indications, original report, clinical history, other imaging modality reports and images and the number of negative and positive cases in the study. Therefore, their results were not based on any previous findings.

Another strength of this research study was that it was the first to be conducted locally. Therefore, it can be used as a small-scale study for larger studies in the future, creating a baseline for further investigations and adding to the body of knowledge.

The results of the study were compared to the gold standard being the histopathological results from biopsy in the pathological cases and a negative follow up imaging for at least 12 months for the normal cases. The fact that the gold standard was used was a strength in the study because the gold standard represented the true disease status of each case.

3.9 Conclusion

The purpose behind this chapter was to outline and represent the research design and the data collection tool adopted in the study and the rationale behind such an approach. The strengths and limitations were acknowledged. The following chapter will exhibit, analyse and discuss the data collected and results obtained.

Chapter 4

Results and Discussions

4.1 Introduction

In this chapter, the analyses and discussion of the data collected is presented. The analyses were performed through a series of statistical tests. Throughout this chapter, the results are discussed in conjunction with the literature findings to achieve the aims of the study proposed in Chapter 1 Section 1.4. Any necessary tables and graphs were utilised to recognise any pattern which provides the best interpretation of results. The IBM SPSS statistical software version 28 (SPSS 28.0) and Microsoft Excel 2022 were used to analyse the data gathered during the study.

4.2 The sample population

4.2.1 Radiologist participation

A total of two from four radiologists who fulfilled the edibility criteria, took part in the study as the other two radiologists had previously been involved in the pilot study and were not included in the actual study. The two radiologists who participated in the study were a breast specialist consultant with more than 10 years of experience and a resident specialist with five years of experience, both of whom individually and blindly reviewed the images.

4.2.2 Patient participation

A total of 35 abbreviated breast MRI scan protocol examinations were evaluated by the two radiologists. The cases were retrospectively selected by the intermediary person from MRI breast examinations performed during the period January 2019 and December 2021. For each radiologist, the order of the cases was randomised, and the radiologists were blinded to the original report, clinical history and other imaging modality reports. To calculate reliability ten of the cases were replicated, resulting in a total of 45 cases.

4.3 Image demographics

4.3.1 Gold standard results

The 35 cases reviewed consisted of 15 negative cases (normal) and 20 positive cases (abnormal). The histological report for the 20 cases identified showed that all had lesions identified by the pathologist as invasive lobular carcinoma with a histology grade of 2. Of these, 13 (65%) were on the left breast and 7 (35%) on the right breast. Out of 20 cases seven (35%) had lymph node involvement.

The gold standard for the normal cases was negative follow up imaging for at least 12 months. The follow-up imaging in these 15 cases were 5 (33.3%) mammography, 5 (33.3%) ultrasound, 4 (26.7%) MRI and 1 (6.7%) DBT.

4.3.2 Patient demographics

The mean patient age of the sample population was 57.9 years with an age range of 27 to 80 years. The indications for MRI were 20 (57.1%) for breast cancer staging, 5 (14.3%) due to nipple discharge with a negative mammogram and ultrasound, 2 (5.7%) for lesion characterisation and 8 (22.9%) for screening due to family history or BRCA mutations.

4.4 Statistical Analysis- ROC curves and AUC results

Applying SPSS statistical software, the ROC curves were constructed for the full and abbreviated protocol (for both radiologists individually) (figures 4.1-4.3) as well as for both radiologists together (figure 4.6) to show the difference in terms of diagnostic accuracy between the full and abbreviated protocol. The gold standard was represented as either 0 or 1 depending if the case is positive (1) or negative (0). The other variables (full and abbreviated) would represent the BI-RADS classification given to each case for the different protocols, with higher numbers indicating greater positivity. The AUC for each curve was obtained together with the p-value (asymptotic significance) of each protocol.

The p value of each model represents if the test is statistically significant. A value of 0.05 or less indicated satisfactory discrimination which means that the test was able to diagnose the disease state at a statistically significant level. The sensitivity, specificity, PPV and NPV were also calculated and compared. The values of the AUC were compared with each other to check for statistical significance by using pairwise comparison design. A p-value (asymptotic significance 2-tail) greater or equal to 0.05 indicates that there is no significant difference between the protocols.

4.4.1 Full protocol analysis

For the full protocol ROC curve (Figure 4.1), the full protocol scores and the gold standard were compared. The AUC value of the ROC curve plotted for the full protocol was 1. This indicates that overall, the full protocol is outstanding in distinguishing between a negative and a positive case since the AUC was 1 which is the maximum AUC value. All the cases in the full protocol were correctly scored when compared to the gold standard and no cases were missed. The accuracy of the full protocol was 100% for all performance indicators (Table 4.1), therefore the full protocol was accurate as the gold standard in diagnosing patients as normal or having a breast cancer present.

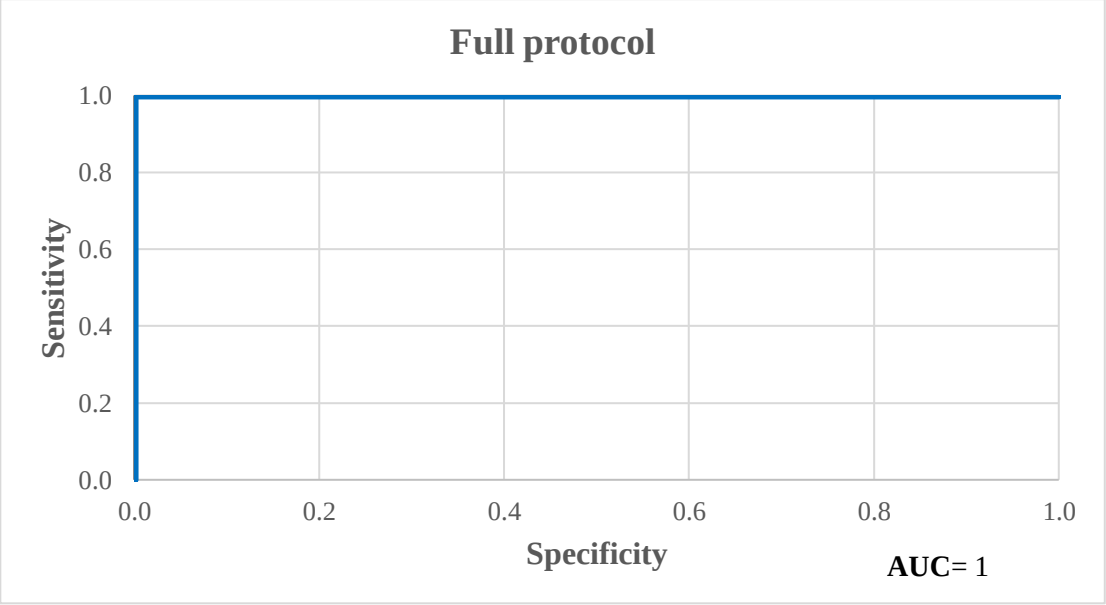


Figure 4.1 ROC curve- Full protocol

Table 4.1 Performance indicators for the full protocol

Performance Indicators	Value
Sensitivity	100%
Specificity	100%
PPV	100%
NPV	100%

4.4.2 Abbreviated protocol analysis (Radiologist A)

For the abbreviated protocol, (radiologist A-consultant) ROC curve (Figure 4.2), the abbreviated protocol scores for radiologist A and the gold standard were compared. Since the full protocol and gold standard agreed 100%, then the full protocol can also be considered as the gold standard. The AUC value of the ROC curve plotted for the abbreviated protocol (radiologist A) was 0.920. The closer the AUC is to the value of 1 means that the test is better at distinguishing between a negative and a positive case and a value of more than 0.9 considers the test outstanding at discrimination (Mandrekar, 2010).

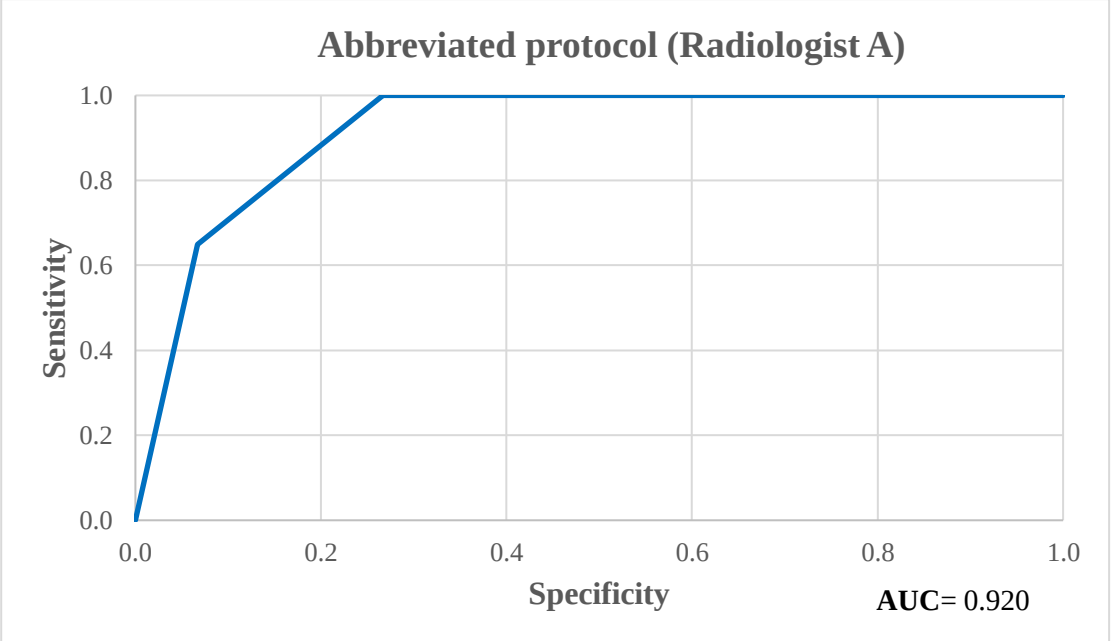


Figure 4.2 ROC curve- Abbreviated protocol (Radiologist A)

Table 4.2 Image ratings by radiologist A

True disease status	1=Negative	2= Benign	3=Probably benign	4= Suspicious	5= Highly suggestive of malignancy	6= Malignancy (biopsy proven)
Normal	4	7	1	2	1	0
Abnormal	0	0	1	6	13	0

Table 4.2 illustrates the ratings of images obtained from the 35 cases by radiologist A. The cut-off point for classifying a patient as normal or abnormal was three therefore, a rating of three or more indicates that the test is positive. From the image ratings it shows that radiologist A scored four normal cases as abnormal. Four cases which were negative were marked as being positive; two cases were marked BI-RADS 4, one BI-RADS 5 and the other BI-RADS 3. There were no positive cases that were missed therefore no breast cancers were missed. The accuracy of the abbreviated protocol for radiologist A was 88.6% (31/35). Performance indicators for Radiologist A are presented in Table 4.3.

Table 4.3 Performance indicators for the abbreviated protocol (radiologist A)

Performance Indicators	**Value**
Sensitivity	100%
Specificity	73.3%
PPV	83.3%
NPV	100%

4.4.3 Abbreviated protocol analysis (Radiologist B)

For the abbreviated protocol (radiologist B- resident specialist) ROC curve (Figure 4.3), the abbreviated protocol scores for radiologist B and the gold standard were compared. The AUC value of the ROC curve plotted for the abbreviated protocol (radiologist B) was 0.922.

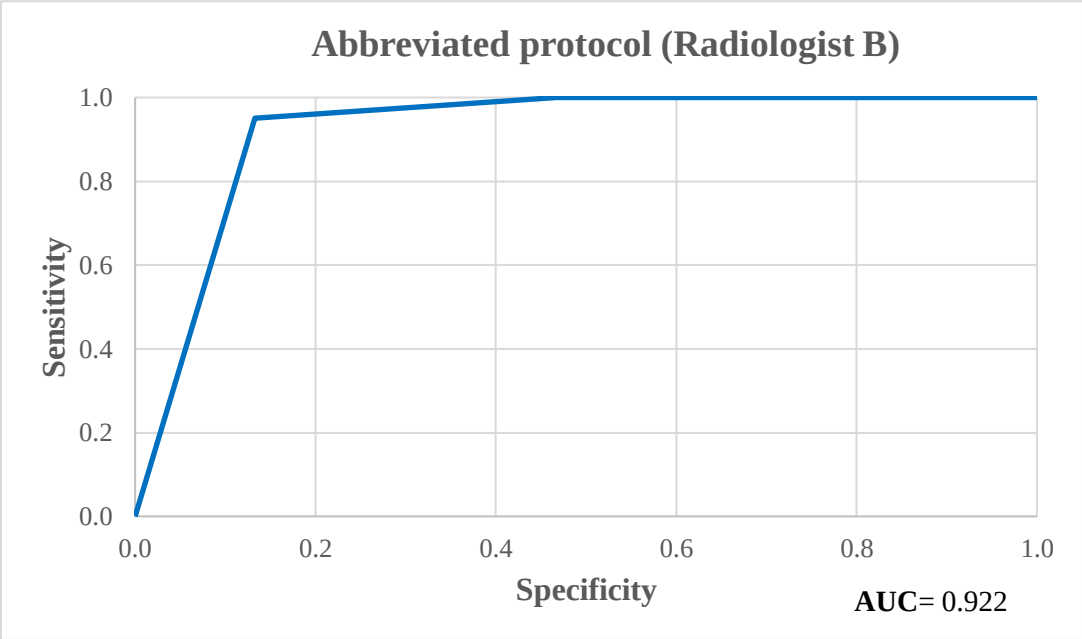


Figure 4.3 ROC curve- Abbreviated protocol (Radiologist B)

Table 4.4 Image ratings by radiologist B

True disease status	1=Negative	2= Benign	3=Probably benign	4= Suspicious	5= Highly suggestive of malignancy	6= Malignancy (biopsy proven)
Normal	8	0	2	3	2	0
Abnormal	0	0	0	1	19	0

The table 4.4 illustrates the ratings of images obtained from the 35 cases by radiologist B. From the image ratings it shows that radiologist B scored seven normal cases as abnormal. Seven cases which were negative were marked as being positive; two cases were marked BI-RADS 5, three BI-RADS 4 and two BI-RADS 3. There were no positive

cases that were missed therefore no breast cancers were missed. The accuracy of the abbreviated protocol for radiologist B was 80% which indicates that when using the abbreviated protocol, radiologist B had accurately classified 28 out of 35 cases correctly. Performance indicators for radiologist B are presented in Table 4.5.

Table 4.5 Performance indicators for the abbreviated protocol (radiologist B)

Performance Indicators	Value
Sensitivity	100%
Specificity	53.5%
PPV	74%
NPV	100%

4.5 Results of lymph nodes, location (right/left breast) and number of lesions

4.5.1 Lymph node involvement

In the current study, lymph node involvement was defined by any presence of disease from the histological result. Similar to the study by Lee-Felker et al. (2020) the same approach was used to assess the detection of lymph nodes when using the abbreviated protocol. In their study Lee-Felker et al., (2020) reported that true positives were histopathological positive lymph nodes when the lymph nodes of the same side were deemed suspicious on MRI while true negatives were those that were histopathological negative when lymph nodes of the same side were normal. False positives were histopathological negative lymph nodes when lymph nodes of the same side were deemed suspicious on MRI and false negatives were histopathological positive lymph node when lymph nodes of the same side were marked as normal on MRI (Lee-Felker et al., 2020). Out of the 20 breast cancer cases seven had histologically proven lymph node metastasis. The results for each protocol for this study are displayed in figures 4.4 and 4.5 for positive and negative lymph node detection respectively.

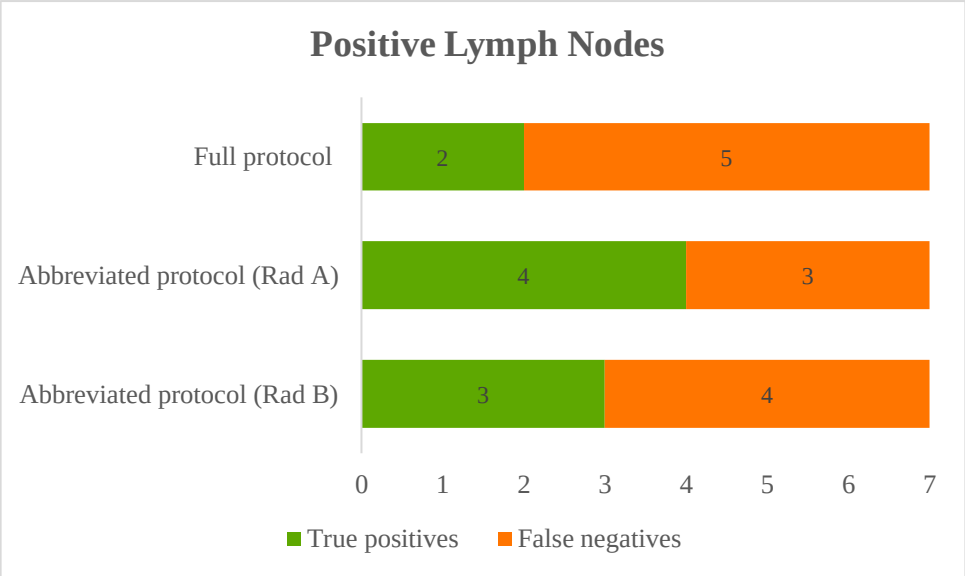


Figure 4.4 Positive lymph nodes detected with all the protocol

The abbreviated protocol observed by radiologist A had the greatest false positives when compared to the other protocols and 4 cases were marked to have positive lymph nodes when they were normal. The abbreviated protocol for radiologist B correctly detected all normal lymph nodes.

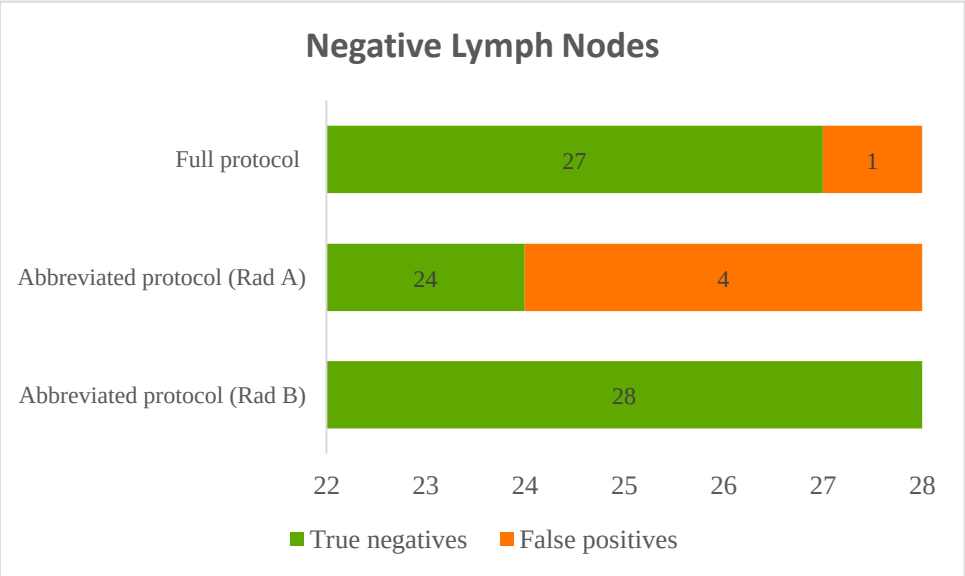


Figure 4.5 Negative lymph nodes detected with all the protocols

4.5.2 Location (right/left breast) and number of lesions

F (Appendix D1). The full protocol detected all lesions on the correct breast while when the abbreviated protocol was used, radiologist A marked two cases as having a lesion on the right breast and two on the left breast, however the cases were normal with no breast cancer. Radiologist B marked four cases to have a lesion on the right and three on the left breast, the cases were normal with no breast cancer. However there was one case where both radiologists marked both breasts to have a pathology, when the breast cancer was only in the left breast.

Besides the location, the number of lesions detected for each positive case was compared to the gold standard to observe if there was agreement (Appendix D1). The full protocol matched the number of lesions for 18 out of 20 positive cases (90%). While the abbreviated protocol for radiologist A and B matched 15 out of 20 positive cases (75%).

4.5.3 Breast localisation and size of lesion

The specific breast location and the size of the lesion could not be accurately assessed because of the inability to correlate the specific location and size with those on the histopathological result, even in retrospect. There are various acronyms for the same specific location either using quadrant, clock-face position or central, retro areolar and axillary tail (Morris et al., 2013). However, when compared to the full protocol, from a total of 20 cases, the abbreviated protocol for radiologist A matched the exact location for 12 cases while radiologist B matched 16 cases (Appendix D2).

The lesion size ideally should be reported in at least two dimensions however three dimensions is preferable especially when comparing to previous examinations (Morris et al., 2013). In this study for both full and abbreviated protocols radiologists would list the size in all three dimensions: anteroposterior (AP), transverse (TRA) and craniocaudal (CC) or only

specify two or one size in a particular direction. Therefore, due to these limitations accurate comparison could not be made however, the data obtained is listed in appendix D2.

4.6 Discussion

4.6.1 AUC value and significance

The AUC obtained from each ROC curve was 1 for the complete protocol, 0.920 and 0.922 for radiologist A and B for the abbreviated protocol respectively. Figure 4.6 shows the ROC curves corresponding to each protocol. The p-value for all the corresponding protocols was <0.05 (Table 4.6) which indicates that each test diagnosed the disease state (cancer yes/no) at a statistically significant level. Thus this indicates that when using the abbreviated protocol the diagnostic accuracy was maintained.

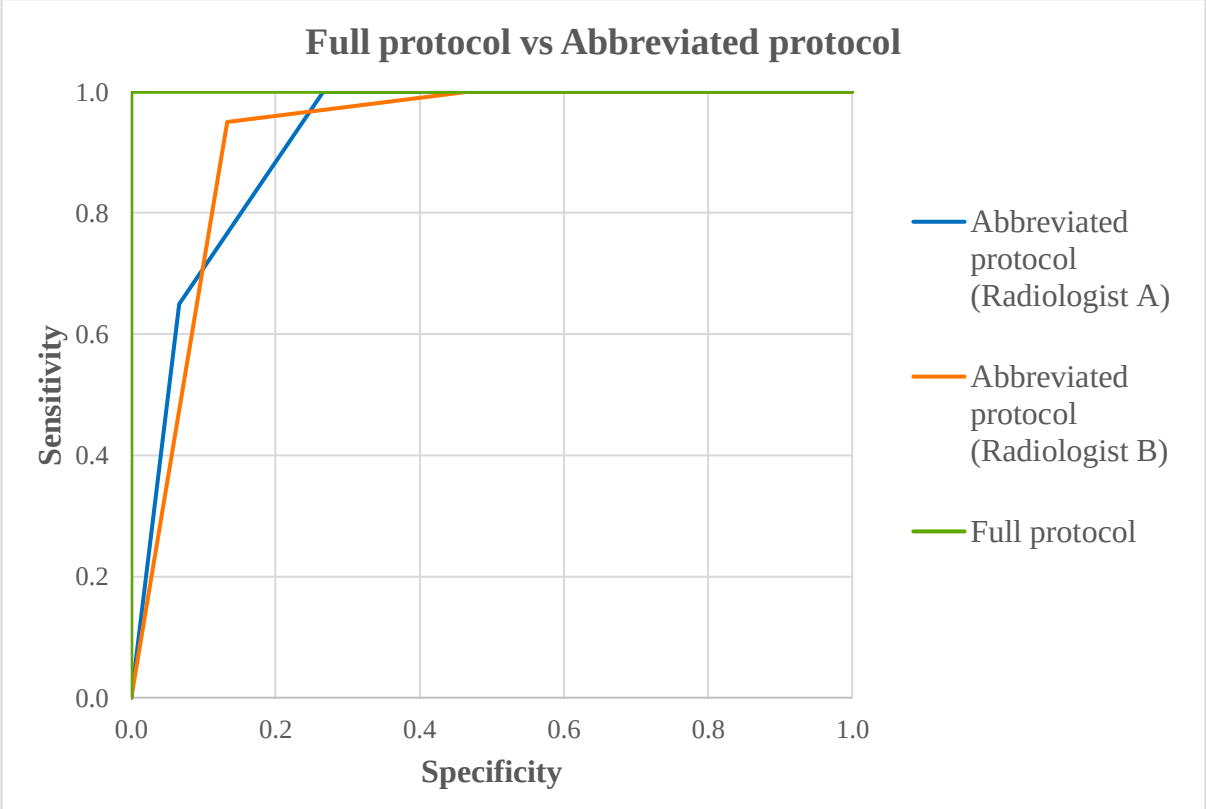


Figure 4.6 ROC curves for full and abbreviated protocols

Table 4.6 Resultant AUC and p-values from ROC curves for both full and abbreviated protocols

Protocol	AUC	p-value (Asymptotic Sig.)	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Full protocol	1.000	0.000	1.000	1.000
Abbreviated protocol (Rad A)	0.920	0.000027	0.818	1.000
Abbreviated protocol (Rad B)	0.922	0.000025	0.814	1.000

When each AUC was compared together, the p-value (asymptotic sig. 2-tail) for each pair was more than 0.05 (Table 4.7) which indicated that there is no significant difference between the protocols. Therefore, there is no significant difference in the effectiveness between the full and abbreviated protocol to diagnose breast cancer. In the ROC study by Martínez et al. (2020) there also was no significant difference observed between the AUC of the complete, abbreviated and MIP protocol (p=0.0650).

Table 4.7 Results from the pairwise comparison of each protocol

Protocol	Asymptotic		AUC difference	Asymptotic 95% Confidence Interval	
	z	Sig. (2-tail)		Lower Bound	Upper Bound
Full protocol vs Abbreviated protocol A	1.646	0.100	0.080	-0.015	0.175
Full protocol vs Abbreviated protocol B	1.620	0.105	0.078	-0.016	0.173
Abbreviated protocol A vs Abbreviated protocol B	-0.037	0.970	-0.002	-0.090	0.087

4.6.2 Sensitivity, Specificity, PPV and NPV

The assessment of the abbreviated protocol for both participating radiologists showed a 100% sensitivity which is the same as that for the full protocol. All cancers were detected by the two radiologists when applying the abbreviated protocol. Studies, such as Heacock et al. (2015) and Mango et al. (2015) have shown that the cancer detection rate was similar when using the abbreviated protocol. Both studies had a similar sample population to the current study, which included biopsy proven cancers. Heacock et al. (2015) all reported that invasive breast cancers were detected with reduced sequences while Mango et al (2015) concluded that all cancers were visualised by at least one of the four readers involved in the study. Petrillo et al. (2017) performed a retrospective study on selected cases and both full and abbreviated protocols detected 206 out of 207 cancers thus there was no difference in diagnostic performance. These comparable findings further support that the abbreviated protocol is effective for cancer detection.

Although the sensitivity of the abbreviated protocol was 100%, the specificity of the abbreviated compared to the full protocol differed substantially. The specificity of the abbreviated protocol was significantly lower for radiologists A and B at 73.3% and 53.5% respectively when compared to that of the full protocol. The low specificity indicates an increase in the false positive rates. False positives are associated with unnecessary further imaging, tissue sampling (biopsy) and additional follow-up examinations to exclude the presence of breast cancer, which could have been avoided (Dekker et al., 2021). Recalls are associated with increased patient anxiety, health care costs and very rarely morbidities related with biopsy (Dekker et al., 2021; Tosteson et al., 2014). Women who had to undergo a biopsy due to a false positive, were 2.3 times less likely to attend future screening within 30 months after the recall (Shen et al., 2017).

Radiologist B had an even lower specificity than radiologist A, this could be due to the fact that this radiologist had less years of experience. The gap between the average expertise in reading mammograms when compared to reading MRI studies may be the reason for the limited specificity of breast MRI imaging (Kuhl, 2007). The study by Kuhl et al. (2014) suggested that the expertise of interpreting radiologists will help to avoid false-positive diagnosis. Radiologists who wish to engage in European screening programs, must report 5000 mammograms per year (Kuhl et al, 2014). Thus, Kuhl et al. (2014) suggests that if an MRI screening program is to be implemented then the radiologic community must undergo the same process it went through with the propagation of mammographic screening process to improve the MRI reporting expertise. In this study, the abbreviated protocol was effective for demonstrating cancers however, 11.4% (4) and 20% (7) normal cases were reported as false positives for radiologist A and B respectively. In the study by Oldrini et al. (2018) the rate of false positives was 4.9% (7) and 8.4% (12) for senior (5 years experience) and junior (6-months experience) radiologists, the number of normal cases missed were much higher than in this study as well as the fact that, the total sample size was much larger (90 women) as opposed to the 35 women in this study. When compared to previous studies (Chen et al., 2017; Machida et al., 2017; Petrillo et al., 2017), the specificity was always slightly lower when compared to the full protocol as observed in Table 2.5. However, reader specificity in the current study was lower than 90% when compared to findings reported in other studies (Kuhl et al., 2014, Moschetta et al., 2016; Panigrahi et al., 2017; Romeo et al., 2017; Oldrini et al., 2018). The reason may be because the radiologists in the current study did not have access to previous imaging and biopsy results therefore, they were unable to confirm long-term stability and correlate any lesion findings with other imaging modalities. The readers in the study by Grimm et al. (2015) did not have access to previous imaging studies and also obtained a low specificity of 45% and 52%.

The ideal test should have both high sensitivity and high specificity and a test can be structured to have a balance between the sensitivity and specificity (Maxim et al., 2014). Maxim et al. (2014) reported the sensitivities and specificities of various screening tests and as can be seen there are a number of screening tests which have both high sensitivity and specificity but many fall short of this ideal as seen in the figure 4.7 below.

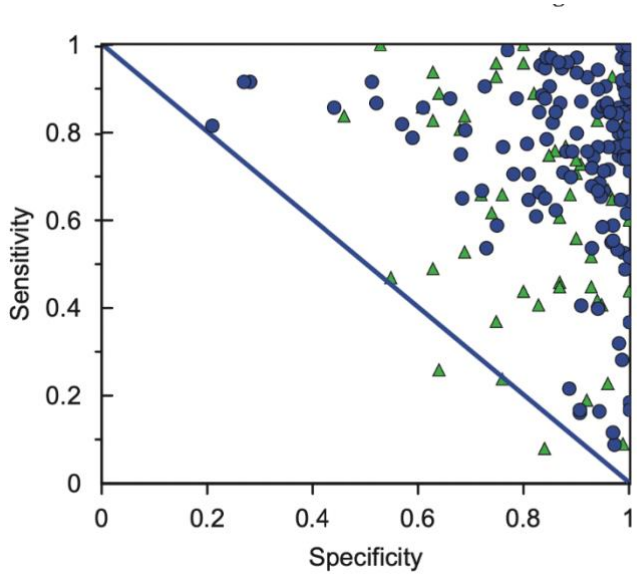


Figure 4.7 Reported sensitivity and specificity of multiple screening tests reported in the study by Maxim et al. (2014) and Alberg et al. (2004).

The high value of the NPV produced by the abbreviated protocol which was 100% for both readers produced strong evidence that the abbreviated protocol was able to exclude the presence of cancer. The NPV was the same for both full and abbreviated protocols which is comparable to other studies (Chen et al., 2017; Kuhl et al., 2014; Machida et al., 2017; Moschetta et al., 2016; Petrillo et al., 2017). The higher the PPV is, the lower the false positive outcomes are (Trevethan, 2017). The PPV value for the full protocol was 100% while that of the abbreviated protocol for radiologist A was 83.3% which was much better than the 74% obtained by radiologist B. In the study by Chen et al. (2017) the PPV value for the abbreviated protocol was also significantly lower than the full protocol with 22 % and 40% respectively.

4.7 Lymph Node involvement

MRI has a limited role in the diagnosis of axillary lymph node metastasis (Marino et al., 2020). There are multiple MRI features which increase suspicion for lymph node metastasis which include loss of fatty hilum, round shape, cortical thickening or a long axis to short axis ratio of less than 2 (Marino et al., 2020). However, perifocal oedema which is demonstrated as a hyperintense signal in the fat surrounding a lymph node on T2 weighted images has a higher PPV value for malignancy (Dogan et al., 2018; Marino et al., 2020). The DWI and unenhanced T1 weighted imaging also provide high accuracy for the detection of lymph node metastasis (Marino et al., 2020). In the study by Strahle et al. (2017) the T1 pre contrast and T1 first and second subtraction images identified lymph nodes much better than T2 and STIR images. In the current research study, the T2 weighted imaging and DWI was not included in the abbreviated protocol however, both abbreviated protocols detected more positive lymph nodes than the full protocol. D

4.8 Conclusion

The data obtained in the current study was presented and discussed in this chapter. This chapter presented an overview of the outcomes of the abbreviated protocol. The advantages and disadvantages of each protocol were highlighted. Overall, there was no significant difference in the diagnostic accuracy (high sensitivity and NPV) between the full and abbreviated protocol to detect breast cancer. However, with the abbreviated protocol a low specificity and PPV value was observed producing a high recall rate and false positives which may complicate the implementation of MRI as a screening tool on a large scale. The conclusions along with further recommendations will be discussed in the following chapter.

Chapter 5

Conclusions and Recommendations

5.1 Introduction

This chapter presents the overall conclusions based on the results acquired from this study and identifies the need for any recommendations for clinical practice or further research on the subject. The conclusions are presented according to the aims and objectives of the research, these are followed by the recommendations for practice drawn from the results and the literature findings.

5.2 Conclusions from the study

The aim of the study was to evaluate and compare the diagnostic accuracy obtained when using an abbreviated protocol against the full protocol for breast MRI imaging in the detection of lobular carcinoma. The study findings do not describe observer performance of abbreviated MRI in non-lobular carcinoma or other breast pathologies. In order to fulfil the aim a number of objectives were set.

Objective 1: The diagnostic accuracy was estimated using standard receiver operating characteristics (ROC) methods. The scores obtained through ROC analysis for both protocols were analysed.

For the full protocol the AUC was 1 which means that the test was perfect in distinguishing between a negative and a positive case. While the abbreviated protocol for radiologist A and B was 0.920 and 0.922 respectively which indicates that the test is outstanding at distinguishing between a negative and a positive case. Each protocol diagnosed the disease state (cancer yes/no) at a statistically significant level (p-value <0.05). This indicates that when using the abbreviated protocol the diagnostic accuracy was maintained. When each AUC was compared together, for each pair the p-value was more than 0.05 which indicates that there is no significant difference between the protocols. There was no significant difference in the effectiveness between the protocols to diagnose breast cancer.

Objective 2: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Sensitivity: Both the full and abbreviated protocols yielded a sensitivity of 100%. All cancers were detected with the abbreviated protocol for both radiologists.

Specificity: The abbreviated protocol for radiologists 1 and 2 had significantly lower specificity of 73.3% and 53.5% respectively than that of the full protocol which was 100%. The low specificity has the disadvantage that subjects who do not have the disease will screen positive and therefore receive unnecessary follow-up tests which may have a potential risk and contribute to increasing costs.

PPV: The PPV value for the full protocol was 100% while that of the abbreviated protocol for radiologist A was 83.3% which was much better than the 74% obtained by radiologist B. Radiologist A had a higher PPV which resulted in lower false positives (n=4) than radiologist B (n=7).

NPV: All protocols produced an NPV value of 100%. The high value of the NPV produced by the abbreviated protocol for both readers produced strong evidence that the abbreviated protocol was able to exclude the presence of cancer.

5.3 Recommendations for clinical practice

The final objective was to propose recommendations for consideration to include the use of an abbreviated MRI breast protocol in the department where the study took place. The data obtained suggested that using the sequences selected, which was based on literature findings, resulted in no significant difference in the diagnostic accuracy when using the abbreviated protocol since all lobular carcinomas were detected.

The abbreviated protocol is an easy and simple technique and there should be no difficulty in implementing this procedure as it is a concise version of the full protocol. No additional equipment or training for the radiographers is needed therefore, no added cost. The abbreviated protocol is associated with decreased scanning time (29 minutes and 1 second reduced scanning times as shown in tabel 3.1) and reading time for the radiologists (Kuhl et al., 2014; Marquina Martínez et al., 2020; Moschetta et al., 2016; Oldrini et al., 2018; Petrillo et al., 2017; Strahle et al., 2017). The abbreviated protocol could enable a higher number of examinations to be performed within the same MR session which could translate into cost-effectiveness and better use of resources (Marquina Martínez et al., 2020; Petrillo et al., 2017).

The dataset used in the current study was based on a symptomatic / non-screening population. Since the selected cases were likely to have been symptomatic or suspicious of malignancy for them to have been referred for an MRI in the first place this could have accounted for the high sensitivity. Therefore, an MRI dataset with the prevalence of disease expected within a high-risk screening population and a wider range of observers should be considered before any further implementation of study findings.

However, when using the abbreviated protocol there was an increase in false positives which would result in incorrect initial diagnosis. This creates additional imaging, scan time or extra biopsies which all come at an extra cost, in conjunction with patient's time and anxiety (Strahle et al., 2017). When implementing a new modality there is a great chance of high false positives rates however, this can be overcome with training and an increase in reporting numbers for the specific abbreviated protocol (Kuhl et al., 2014). Further training to radiologists is required as stated by Pham et al. (2020), to ensure that a more uniform threshold is used when determining the need to recall patients for an abnormality.

Locally the use of the abbreviated protocol could first be implemented for women who have a high-risk of developing breast cancer with the long-term goal being to increase the widespread use of MR for the whole screening population.

5.4 Recommendations for further research

As this study had a small population sample, which has been acknowledged as a major limitation of the study, it is recommended that the study is repeated on a wider scale to assess if the results remain the same over a larger sample of cases.

In the current study only lobular carcinoma was included as a type of breast cancer therefore, an extension of the study could be that other types of breast cancers are included in the sample population. Then the effectiveness of the abbreviated protocol can be assessed over the different breast cancer types.

An extension to this study is to investigate the reading times of the radiologist and how it would change when reporting the abbreviated protocol locally. This could be compared to the reading times of mammography, US or DBT.

The abbreviated protocol could be investigated for the general screening population because in this study, due to the small sample size the population sample did not represent only the screening population.

The study of women's attitudes and opinion towards the use of an abbreviated MRI protocol as a screening tool for breast cancer instead of or additional to mammography, US or DBT could also be investigated.

5.5 Conclusion

The conclusions of the current research study were presented in this chapter and relative recommendations were suggested. The abbreviated protocol is the future for screening with MRI. Locally, this research study was the first of its kind to be performed

creating a baseline for further investigations and adding to the body of knowledge. The current study with its limitations, demonstrated that the abbreviated protocol had an equal diagnostic accuracy to that of the full protocol indicating promising results for any future studies.

Word Count: 27,321

Reference List

Abe, H., Mori, N., Tsuchiya, K., Schacht, D. V., Pineda, F. D., Jiang, Y., & Karczmar, G. S. (2016). Kinetic Analysis of Benign and Malignant Breast Lesions With Ultrafast Dynamic Contrast-Enhanced MRI: Comparison With Standard Kinetic Assessment. *American Journal of Roentgenology*, *207*(5), 1159–1166. https://doi.org/10.2214/AJR.15.15957

Abutabenjeh, S., & Jaradat, R. (2018). Clarification of research design, research methods, and research methodology: A guide for public administration researchers and practitioners. *Teaching Public Administration*, *36*(3), 237–258. https://doi.org/10.1177/0144739418775787

Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge of breast cancer. *Biological Research*, *50*(1), 33. https://doi.org/10.1186/s40659-017-0140-9

Alberg, A. J., Park, J. W., Hager, B. W., Brock, M. V., & Diener-West, M. (2004). The use of "overall accuracy" to evaluate the validity of screening or diagnostic tests. *Journal of General Internal Medicine*, *19*(5), 460–465. https://doi.org/10.1111/j.1525-1497.2004.30091.x

Albert, M., Schnabel, F., Chun, J., Schwartz, S., Lee, J., Klautau Leite, A. P., & Moy, L. (2015). The relationship of breast density in mammography and magnetic resonance imaging in high-risk women and women with breast cancer. *Clinical Imaging*, *39*(6), 987–992. https://doi.org/10.1016/j.clinimag.2015.08.001

Alkabban, F. M., & Ferguson, T. (2022). Breast Cancer. In *StatPearls*. StatPearls Publishing. PMID: 29493913.

Al-Mousa, D. S., Alakhras, M., Spuur, K. M., Alewaidat, H., Abdelrahman, M., Rawashdeh, M., & Brennan, P. C. (2020). The implications of increased mammographic breast

density for breast screening in Jordan. *Journal of Medical Radiation Sciences*, *67*(4), 277–283. https://doi.org/10.1002/jmrs.414

American Cancer Society. *Breast Cancer Facts & Figures 2019-2020*. Atlanta: American Cancer Society, Inc. 2019.

American College of Radiology (2003) BI-RADS - Mammography, Fourth Edition. Retrieved: April 28th,2021 from http://www.acr.org/QualitySafety/Resources/BI-RADS/Mammography American College of Radiology.

Amornsiripanitch, N., Bickelhaupt, S., Shin, H. J., Dang, M., Rahbar, H., Pinker, K., & Partridge, S. C. (2019). Diffusion-weighted MRI for Unenhanced Breast Cancer Screening. *Radiology*, *293*(3), 504–520. https://doi.org/10.1148/radiol.2019182789

Aristokli, N., Polycarpou, I., Themistocleous, S. C., Sophocleous, D., & Mamais, I. (2022). Comparison of the diagnostic performance of Magnetic Resonance Imaging (MRI), ultrasound and mammography for detection of breast cancer based on tumor type, breast density and patient's history: A review. *Radiography*, *28*(3), 848–856. https://doi.org/10.1016/j.radi.2022.01.006

Arleo, E. K., Hendrick, R. E., Helvie, M. A., & Sickles, E. A. (2017). Comparison of recommendations for screening mammography using CISNET models: Screening Mammography Recommendations. *Cancer*, *123*(19), 3673–3680. https://doi.org/10.1002/cncr.30842

Arnold, M., Morgan, E., Rumgay, H., Mafra, A., Singh, D., Laversanne, M., Vignat, J., Gralow, J. R., Cardoso, F., Siesling, S., & Soerjomataram, I. (2022). Current and future burden of breast cancer: Global statistics for 2020 and 2040. *The Breast*, *66*, 15–23. https://doi.org/10.1016/j.breast.2022.08.010

Arpino, G., Laucirica, R., & Elledge, R. M. (2005). Premalignant and In Situ Breast Disease: Biology and Clinical Implications. *Annals of Internal Medicine*, *143*(6), 446. https://doi.org/10.7326/0003-4819-143-6-200509200-00009

Artstein, R., & Poesio, M. (2008). Inter-coder agreement for computational linguistics.

Bakker, M. F., de Lange, S. V., Pijnappel, R. M., Mann, R. M., Peeters, P. H. M., Monninkhof, E. M., Emaus, M. J., Loo, C. E., Bisschops, R. H. C., Lobbes, M. B. I., de Jong, M. D. F., Duvivier, K. M., Veltman, J., Karssemeijer, N., de Koning, H. J., van Diest, P. J., Mali, W. P. T. M., van den Bosch, M. A. A. J., Veldhuis, W. B., & van Gils, C. H. (2019). Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. *New England Journal of Medicine*, *381*(22), 2091–2102. https://doi.org/10.1056/NEJMoa1903986

Baltzer, P. A. T., Bickel, H., Spick, C., Wengert, G., Woitek, R., Kapetas, P., Clauser, P., Helbich, T. H., & Pinker, K. (2018). Potential of Noncontrast Magnetic Resonance Imaging With Diffusion-Weighted Imaging in Characterization of Breast Lesions: Intraindividual Comparison With Dynamic Contrast-Enhanced Magnetic Resonance Imaging. Investigative radiology, 53(4), 229–235. https://doi.org/10.1097/RLI.0000000000000433

Balmaña, J., Díez, O., Rubio, I. T., & Cardoso, F. (2011). BRCA in breast cancer: ESMO Clinical Practice Guidelines. *Annals of Oncology*, *22*, vi31–vi34. https://doi.org/10.1093/annonc/mdr373

Baratloo, A., Hosseini, M., & Negida, A. (2015). *Part 1: Simple Definition and Calculation of Accuracy, Sensitivity and Specificity*.

Beau, A.-B., Andersen, P. K., Vejborg, I., & Lynge, E. (2018). Limitations in the Effect of Screening on Breast Cancer Mortality. *Journal of Clinical Oncology*, *36*(30), 2988–2994. https://doi.org/10.1200/JCO.2018.78.0270

Berg, W. A., Zhang, Z., Lehrer, D., Jong, R. A., Pisano, E. D., & Barr, R. G. (2012). *Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk*. 11.

Bevers, T. B., Anderson, B. O., Bonaccio, E., Buys, S., Daly, M. B., Dempsey, P. J., Farrar, W. B., Fleming, I., Garber, J. E., Harris, R. E., Heerdt, A. S., Helvie, M., Huff, J. G., Khakpour, N., Khan, S. A., Krontiras, H., Lyman, G., Rafferty, E., & Shaw, S. (2009). *Breast Cancer Screening and Diagnosis Clinical Practice Guidelines in Oncology*. *7*(2), 242. https://doi.org/10.6004/jnccn.2003.0023

Bickelhaupt, S., Laun, F. B., Tesdorff, J., Lederer, W., Daniel, H., Stieber, A., Delorme, S., & Schlemmer, H.-P. (2016). Fast and Noninvasive Characterization of Suspicious Lesions Detected at Breast Cancer X-Ray Screening: Capability of Diffusion-weighted MR Imaging with MIPs. *Radiology*, *278*(3), 689–697. https://doi.org/10.1148/radiol.2015150425

Biomedical, U. S. N. C. for the P. of H. S. of, & Research, B. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. The Commission. https://books.google.com.mt/books?id=wjlrAAAAMAAJ

Bleyer, A., & Welch, H. G. (2012). Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence. *New England Journal of Medicine*, *367*(21), 1998–2005. https://doi.org/10.1056/NEJMoa1206809

Boca (Bene), I., Ciurea, A. I., Ciortea, C. A., & Dudea, S. M. (2021). Pros and Cons for Automated Breast Ultrasound (ABUS): A Narrative Review. *Journal of Personalized Medicine*, *11*(8), 703. https://doi.org/10.3390/jpm11080703

Borg, B (2022, March 11). Labour's election manifesto at-a-glance: What is the party proposing? Times of Malta. Accessed 11 May 2022 from https://timesofmalta.com/articles/view/labours-election-manifesto-at-a-glance-what-is-the-party-proposing.940737Computational Linguistic, 34(4), 555-596.

Bravi, F., Decarli, A., & Russo, A. G. (2018). Risk factors for breast cancer in a cohort of mammographic screening program: A nested case-control study within the FRiCaM study. *Cancer Medicine*, *7*(5), 2145–2152. https://doi.org/10.1002/cam4.1427

Bretthauer, M., & Kalager, M. (2013). Principles, effectiveness and caveats in screening for cancer. The British journal of surgery, 100(1), 55–65. https://doi.org/10.1002/bjs.8995

Brewer, H. R., Jones, M. E., Schoemaker, M. J., Ashworth, A., & Swerdlow, A. J. (2017). Family history and risk of breast cancer: An analysis accounting for family structure. *Breast Cancer Research and Treatment*, *165*(1), 193–200. https://doi.org/10.1007/s10549-017-4325-2

Byrne, C., Ursin, G., Martin, C. F., Peck, J. D., Cole, E. B., Zeng, D., Kim, E., Yaffe, M. D., Boyd, N. F., Heiss, G., McTiernan, A., Chlebowski, R. T., Lane, D. S., Manson, J. E., Wactawski-Wende, J., & Pisano, E. D. (2017). Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk. *JNCI: Journal of the National Cancer Institute*, *109*(9). https://doi.org/10.1093/jnci/djx001

Cadiz, F., Kuerer, H. M., Puga, J., Camacho, J., Cunill, E., & Arun, B. (2013). Establishing a Program for Individuals at High Risk for Breast Cancer. *Journal of Cancer*, *4*(5), 433–446. https://doi.org/10.7150/jca.6481

Carney, P. A., Miglioretti, D. L., Yankaskas, B. C., Kerlikowske, K., Rosenberg, R., Rutter, C. M., Geller, B. M., Abraham, L. A., Taplin, S. H., Dignan, M., Cutter, G., &

Ballard-Barbash, R. (2003). Individual and Combined Effects of Age, Breast Density, and Hormone Replacement Therapy Use on the Accuracy of Screening Mammography. *Annals of Internal Medicine*, *138*(3), 168. https://doi.org/10.7326/0003-4819-138-3-200302040-00008

Checka, C. M., Chun, J. E., Schnabel, F. R., Lee, J., & Toth, H. (2012). The Relationship of Mammographic Density and Age: Implications for Breast Cancer Screening. *Breast Cancer Screening*, 4.

Chen, J.-H., Gulsen, G., & Su, M.-Y. (2015). Imaging Breast Density: Established and Emerging Modalities. *Translational Oncology*, *8*(6), 435–445. https://doi.org/10.1016/j.tranon.2015.10.002

Chen, S.-Q., Huang, M., Shen, Y.-Y., Liu, C.-L., & Xu, C.-X. (2017). Application of Abbreviated Protocol of Magnetic Resonance Imaging for Breast Cancer Screening in Dense Breast Tissue. *Academic Radiology*, *24*(3), 316–320. https://doi.org/10.1016/j.acra.2016.10.003

Chhor, C. M., & Mercado, C. L. (2017). Abbreviated MRI Protocols: Wave of the Future for Breast Cancer Screening. *American Journal of Roentgenology*, *208*(2), 284–289. https://doi.org/10.2214/AJR.16.17205

Choi, B. H., Choi, N., Kim, M. Y., Yang, J.-H., Yoo, Y. B., & Jung, H. K. (2018). Usefulness of abbreviated breast MRI screening for women with a history of breast cancer surgery. *Breast Cancer Research and Treatment*, *167*(2), 495–502. https://doi.org/10.1007/s10549-017-4530-z

Chong, A., Weinstein, S. P., McDonald, E. S., & Conant, E. F. (2019). Digital Breast Tomosynthesis: Concepts and Clinical Practice. *Radiology*, *292*(1), 1–14. https://doi.org/10.1148/radiol.2019180760

Cobain, E. F., Milliron, K. J., & Merajver, S. D. (2016). Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. *Seminars in Oncology*, *43*(5), 528–535. https://doi.org/10.1053/j.seminoncol.2016.10.001

Coop, P., Cowling, C., & Lawson, C. (2016). Tomosynthesis as a screening tool for breast cancer: A systematic review. *Radiography*, *22*(3), e190–e195. https://doi.org/10.1016/j.radi.2016.03.002

Comstock, C. E., Gatsonis, C., Newstead, G. M., Snyder, B. S., Gareen, I. F., Bergin, J. T., Rahbar, H., Sung, J. S., Jacobs, C., Harvey, J. A., Nicholson, M. H., Ward, R. C., Holt, J., Prather, A., Miller, K. D., Schnall, M. D., & Kuhl, C. K. (2020). Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women With Dense Breasts Undergoing Screening. JAMA, 323(8), 746–756. https://doi.org/10.1001/jama.2020.0572

Conley, C. (2017). *Decision-Making among Women at High Risk for Breast Cancer: Complementary Roles of Emotion and Cognition*.

Cormack, D., Gerrish, K., & Lathlean, J. (2015). *The Research Process in Nursing* (7th ed.). John Wiley & Sons, Ltd.

Cortesi, L., Barbieri, E., & Toss, A. (2019). Breast ultrasound in high-risk women. *Oncotarget*, *10*(16), 1552–1553. https://doi.org/10.18632/oncotarget.26713

Darby, S., McGale, P., & Correa, C. (2011). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *The Lancet*, *378*(9804), 1707–1716. https://doi.org/10.1016/S0140-6736(11)61629-2

Koning, H. J. (2003). Mammographic screening: Evidence from randomised controlled trials. *Annals of Oncology*, *14*(8), 1185–1189. https://doi.org/10.1093/annonc/mdg319

De Silva, S., Tennekoon, K. H., & Karunanayake, E. H. (2019). Overview of the genetic basis toward early detection of breast cancer. *Breast Cancer: Targets and Therapy*, *Volume 11*, 71–80. https://doi.org/10.2147/BCTT.S185870

Deike-Hofmann, K., Koenig, F., Paech, D., Dreher, C., Delorme, S., Schlemmer, H.-P., & Bickelhaupt, S. (2019). Abbreviated MRI Protocols in Breast Cancer Diagnostics: Abbreviated Breast MRI. *Journal of Magnetic Resonance Imaging*, *49*(3), 647–658. https://doi.org/10.1002/jmri.26525

Dekkers, I. A., Roos, R., & van der Molen, A. J. (2018). Gadolinium retention after administration of contrast agents based on linear chelators and the recommendations of the European Medicines Agency. *European Radiology*, *28*(4), 1579–1584. https://doi.org/10.1007/s00330-017-5065-8

Dellis, A., Skolarikos, A., & Papatsoris, A. G. (2014). Why should I do research? Is it a waste of time? *Arab Journal of Urology*, *12*(1), 68–70. https://doi.org/10.1016/j.aju.2013.08.007

DeMartini, W. B., Liu, F., Peacock, S., Eby, P. R., Gutierrez, R. L., & Lehman, C. D. (2012). Background Parenchymal Enhancement on Breast MRI: Impact on Diagnostic Performance. *American Journal of Roentgenology*, *198*(4), W373–W380. https://doi.org/10.2214/AJR.10.6272

Den Dekker, B. M., Bakker, M. F., de Lange, S. V., Veldhuis, W. B., van Diest, P. J., Duvivier, K. M., Lobbes, M. B. I., Loo, C. E., Mann, R. M., Monninkhof, E. M., Veltman, J., Pijnappel, R. M., van Gils, C. H., For the DENSE Trial Study Group, van Gils, C. H., Bakker, M. F., de Lange, S. V., Veenhuizen, S. G. A., Veldhuis, W.

B., … de Koning, H. J. (2021). Reducing False-Positive Screening MRI Rate in Women with Extremely Dense Breasts Using Prediction Models Based on Data from the DENSE Trial. *Radiology*, *301*(2), 283–292. https://doi.org/10.1148/radiol.2021210325

Department of Health Information and Research- Malta National Cancer Registry. (2019). Female Breast Cancer. Retrieved March 20,2023, from http://deputyprimeminister.gov.mt/en/dhir/Documents/Cancer/2020/cancers%20pdfs/Breast 2017.pdf.

Dogan, B. E., Scoggins, M. E., Son, J. B., Wei, W., Candelaria, R., Yang, W. T., & Ma, J. (2018). American College of Radiology–Compliant Short Protocol Breast MRI for High-Risk Breast Cancer Screening: A Prospective Feasibility Study. *American Journal of Roentgenology*, *210*(1), 214–221. https://doi.org/10.2214/AJR.17.18267

Dontchos, B. N., Rahbar, H., Partridge, S. C., Lehman, C. D., & DeMartini, W. B. (2019). Influence of Menstrual Cycle Timing on Screening Breast MRI Background Parenchymal Enhancement and Diagnostic Performance in Premenopausal Women. *Journal of Breast Imaging*, *1*(3), 205–211. https://doi.org/10.1093/jbi/wbz022

D'Orsi CJ, Sickles EA, Mendelson EB et al. (2013) ACR BI-RADS ® Atlas, Breast Imaging Reporting and Data System. American College of Radiology, Reston, VA

Drukteinis, J. S., Mooney, B. P., Flowers, C. I., & Gatenby, R. A. (2013). Beyond Mammography: New Frontiers in Breast Cancer Screening. *The American Journal of Medicine*, *126*(6), 472–479. https://doi.org/10.1016/j.amjmed.2012.11.025

Duffy, S. W., Morrish, O. W. E., Allgood, P. C., Black, R., Gillan, M. G. C., Willsher, P., Cooke, J., Duncan, K. A., Michell, M. J., Dobson, H. M., Maroni, R., Lim, Y. Y., Purushothaman, H. N., Suaris, T., Astley, S. M., Young, K. C., Tucker, L., & Gilbert,

F. J. (2018). Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. *European Journal of Cancer, 88,* 48–56. https://doi.org/10.1016/j.ejca.2017.10.022

Elfil, M., & Negida, A. (2017). *Sampling methods in Clinical Research; an Educational Review*. 3.

Ellis, R. L. (2009). Optimal Timing of Breast MRI Examinations for Premenopausal Women Who Do Not Have a Normal Menstrual Cycle. *American Journal of Roentgenology*, *193*(6), 1738–1740. https://doi.org/10.2214/AJR.09.2657

Elmore, J. G., & Lee, C. I. (2020). What Do the European Breast Cancer Screening Guidelines Portend for U.S. Practice? *Annals of Internal Medicine*, *172*(1), 65. https://doi.org/10.7326/M19-3104

European Commission Initiative on Breast Cancer (ECIBC) (2022) Retrieved: April 28th,2022 from https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies

Eurostat. (2018, April). Breast cancer screening statistics. Retrieved 16th November, 2022, from European commission Eurostat: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Archive:Breast_cancer_screening_statistics&oldid=379969

Eurostat. (2020, August). Causes of death — malignant neoplasms of breast, residents. Retrieved 16th November, 2022 from European commission Eurostat:. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Causes_of_death_—_malignant_neoplasms_of_breast,_residents,_2017_Health20.png

Feig, S. (2010). Cost-Effectiveness of Mammography, MRI, and Ultrasonography for Breast Cancer Screening. *Radiologic Clinics of North America*, *48*(5), 879–891. https://doi.org/10.1016/j.rcl.2010.06.002

Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., Ji, X., Liu, W., Huang, B., Luo, W., Liu, B., Lei, Y., Du, S., Vuppalapati, A., Luu, H. H., Haydon, R. C., He, T.-C., & Ren, G. (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & Diseases*, *5*(2), 77–106. https://doi.org/10.1016/j.gendis.2018.05.001

Franceschini G, Di Leone A, Terribile D, Sanchez MA, Masetti R. Bilateral prophylactic mastectomy in BRCA mutation carriers: what surgeons need to know. Ann Ital Chir. 2019;90:1-2. PMID: 30872561.

Freer, P. E. (2015). *Mammographic Breast Density: Impact on Breast Cancer Risk and Implications for Screening*. *35*(2), 14.

Gail, M. H., & Pfeiffer, R. M. (2005). On criteria for evaluating models of absolute risk. *Biostatistics*, *6*(2), 227–239. https://doi.org/10.1093/biostatistics/kxi005

Gao, Y., Reig, B., Heacock, L., Bennett, D. L., Heller, S. L., & Moy, L. (2021). Magnetic Resonance Imaging in Screening of Breast Cancer. Radiologic clinics of North America, 59(1), 85–98. https://doi.org/10.1016/j.rcl.2020.09.004

Gethin, G and Clune-Mulvaney, C (2009) Understanding Research. Wounds UK, 5(4), 111-115.

Ghaderi, K. F., Phillips, J., Perry, H., Lotfi, P., & Mehta, T. S. (2019). Contrast-enhanced

Gerrish, K., & Lacey, A. (2010). *The Research Process in Nursing*. Blackwell Publishing. https://books.google.com.mt/books?id=_PL0N921VMC&printsec=frontcover&source=gbs_vpt_reviews#v=onepage&q=prospective&f=false

Mammography: Current Applications and Future Directions. *RadioGraphics*, *39*(7), 1907–1920. https://doi.org/10.1148/rg.2019190079

Ghadimi, M., & Sapra, A. (2019). *Magnetic Resonance Imaging (MRI), Contraindications*. 6.

Ghaemian, N., Haji Ghazi Tehrani, N., & Nabahati, M. (2021). Accuracy of mammography and ultrasonography and their BI-RADS in detection of the breast malignancies. *Caspian Journal of Internal Medicine*, *12*(4). https://doi.org/10.22088/cjim.12.4.573

Gray, J., Susan K. Grove, & Suzanne Sutherland. (2017). *Burns and Grove's the Practice of Nursing Research: Appraisal, Synthesis, and Generation of Evidence*. Elsevier. https://books.google.com.mt/books?id=1KmtjwEACAAJ

Greenwood, H. I. (2019). Abbreviated protocol breast MRI: The past, present, and future. *Clinical Imaging*, *53*, 169–173. https://doi.org/10.1016/j.clinimag.2018.10.017

Grimm, L. J., Soo, M. S., Yoon, S., Kim, C., Ghate, S. V., & Johnson, K. S. (2015). Abbreviated Screening Protocol for Breast MRI. *Academic Radiology*, *22*(9), 1157–1162. https://doi.org/10.1016/j.acra.2015.06.004

Grove, S., Burns, N., & Gray, J. (2013). *The practice of nursing research* (7th ed.). St. Louis, Mo: Elsevier/Saunders.

Grove, S. K., & Gray, J. R. (2013). *Building an Evidence-Based Practice*. 652.

Gulani, V., Calamante, F., Shellock, F. G., Kanal, E., & Reeder, S. B. (2017). Gadolinium deposition in the brain: Summary of evidence and recommendations. *The Lancet Neurology*, *16*(7), 564–570. https://doi.org/10.1016/S1474-4422(17)30158-8

Gunduru, M., & Grigorian, C. (2021). Breast Magnetic Resonance Imaging. In *StatPearls*. StatPearls Publishing. (https://www.ncbi.nlm.nih.gov/books/NBK539727/)

Gupta, D., Wang, L., & Friedewald, S. (2017). Breast MRI: Standard Terminologies and Reporting. In S. L. Heller & L. Moy (Eds.), *Breast Oncology: Techniques, Indications, and Interpretation* (pp. 25–46). Springer International Publishing. https://doi.org/10.1007/978-3-319-42563-4_2

Hajian-Tilaki K. (2013). Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian journal of internal medicine*, *4*(2), 627–635.

Hartwig, V., Giovannetti, G., Vanello, N., Lombardi, M., Landini, L., & Simi, S. (2009). Biological Effects and Safety in Magnetic Resonance Imaging: A Review. *International Journal of Environmental Research and Public Health*, *6*(6), 1778–1798. https://doi.org/10.3390/ijerph6061778

Harvey, S. C., Di Carlo, P. A., Lee, B., Obadina, E., Sippo, D., & Mullen, L. (2016). An Abbreviated Protocol for High-Risk Screening Breast MRI Saves Time and Resources. *Journal of the American College of Radiology*, *13*(11), R74–R80. https://doi.org/10.1016/j.jacr.2016.09.031

Hashem, L. M. B., Abd El Hamid, N. O., Kamal, R. M., Mansour, S. M., Lasheen, S., & Tohamey, Y. M. (2021). Does contrast-enhanced mammography have an impact on the detection of cancer in patients with risk of developing breast cancer? *Egyptian Journal of Radiology and Nuclear Medicine*, *52*(1), 71. https://doi.org/10.1186/s43055-021-00447-8

Haussmann, J., Corradini, S., Nestle-Kraemling, C., Bölke, E., Njanang, F. J. D., Tamaskovics, B., Orth, K., Ruckhaeberle, E., Fehm, T., Mohrmann, S., Simiantonakis, I., Budach, W., & Matuschek, C. (2020). Recent advances in radiotherapy of breast cancer. *Radiation Oncology*, *15*(1), 71. https://doi.org/10.1186/s13014-020-01501-x

Haygood, T. M., Wang, J., Atkinson, E. N., Lane, D., Stephens, T. W., Patel, P., & Whitman, G. J. (2009). Timed Efficiency of Interpretation of Digital and Film-Screen Screening Mammograms. *American Journal of Roentgenology*, *192*(1), 216–220. https://doi.org/10.2214/AJR.07.3608

Heacock, L., Melsaether, A. N., Heller, S. L., Gao, Y., Pysarenko, K. M., Babb, J. S., Kim, S. G., & Moy, L. (2016). Evaluation of a known breast cancer using an abbreviated breast MRI protocol: Correlation of imaging characteristics and pathology with lesion detection and conspicuity. *European Journal of Radiology*, *85*(4), 815–823. https://doi.org/10.1016/j.ejrad.2016.01.005

Hermann, N., Klil-Drori, A., Angarita, F. A., Westergard, S., Freitas, V., Scaranelo, A., McCready, D. R., & Cil, T. D. (2020). Screening women at high risk for breast cancer: One program fits all?: Subgroup analysis of a large population high risk breast screening program. *Breast Cancer Research and Treatment*, *184*(3), 763–770. https://doi.org/10.1007/s10549-020-05895-w

Hilal, T., & Rudy, D. W. (2016). *Radiation-induced breast cancer: The question of early breast cancer screening in Hodgkin's lymphoma survivors*. 2.

Ji, Y., Li, B., Zhao, R., Zhang, Y., Liu, J., & Lu, H. (2021). The relationship between breast density, age, and mammographic lesion type among Chinese breast cancer patients from a large clinical dataset. *BMC Medical Imaging*, *21*(1), 43. https://doi.org/10.1186/s12880-021-00565-9

Johnson, B., & Christensen, L. (2012). *Educational research* (4th ed.). London, United Kingdom: SAGE Publications Ltd.

Jones, E. F., Hathi, D. K., Freimanis, R., Mukhtar, R. A., Chien, A. J., Esserman, L. J., van't Veer, L. J., Joe, B. N., & Hylton, N. M. (2020). Current Landscape of Breast Cancer

Imaging and Potential Quantitative Imaging Markers of Response in ER-Positive Breast Cancers Treated with Neoadjuvant Therapy. *Cancers*, *12*(6), 1511. https://doi.org/10.3390/cancers12061511

Joy, J. E., Penhoet, E. E., Petitti, D. B., & Institute of Medicine (US) and National Research Council (US) Committee on New Approaches to Early Detection and Diagnosis of Breast Cancer (Eds.). (2005). *Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis*. National Academies Press (US).

Kamińska, M., Ciszewski, T., Łopacka-Szatan, K., Miotła, P., & Starosławska, E. (2015). Breast cancer risk factors. *Menopausal Review*, *3*, 196–202. https://doi.org/10.5114/pm.2015.54346

Kazama, T., Kuroki, Y., Kikuchi, M., Sato, Y., Nagashima, T., Miyazawa, Y., Sakakibara, M., Kaneoya, K., Makimoto, Y., Hashimoto, H., Motoori, K., & Takano, H. (2012). Diffusion-weighted MRI as an adjunct to mammography in women under 50 years of age: An initial study. *Journal of Magnetic Resonance Imaging*, *36*(1), 139–144. https://doi.org/10.1002/jmri.23626

Kelemen, L. E., Pankratz, V. S., Sellers, T. A., Brandt, K. R., Wang, A., Janney, C., Fredericksen, Z. S., Cerhan, J. R., & Vachon, C. M. (2008). Age-specific Trends in Mammographic Density: The Minnesota Breast Cancer Family Study. *American Journal of Epidemiology*, *167*(9), 1027–1036. https://doi.org/10.1093/aje/kwn063

Kim, S. H., Kim, H. H., & Moon, W. K. (2020). Automated Breast Ultrasound Screening for Dense Breasts. *Korean Journal of Radiology*, *21*(1), 15. https://doi.org/10.3348/kjr.2019.0176

Ko, E. S., & Morris, E. A. (2019). Abbreviated Magnetic Resonance Imaging for Breast Cancer Screening: Concept, Early Results, and Considerations. *Korean Journal of Radiology*, *20*(4), 533. https://doi.org/10.3348/kjr.2018.0722

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, *15*(2), 155–163. https://doi.org/10.1016/j.jcm.2016.02.012

Kriege, M., Brekelmans, C. T. M., Zonderland, H. M., Kok, T., & Meijer, S. (2004). Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition. *The New England Journal of Medicine*, 11.

Kuhl, C. (2007). The Current Status of Breast MR Imaging Part I. Choice of Technique, Image Interpretation, Diagnostic Accuracy, and Transfer to Clinical Practice. *Radiology*, *244*(2), 356–378. https://doi.org/10.1148/radiol.2442051620

Kuhl, C. K. (2018). Abbreviated breast MRI for screening women with dense breast: The EA1141 trial. *The British Journal of Radiology*, *91*(1090), 20170441. https://doi.org/10.1259/bjr.20170441

Kuhl, C. K. (2019). Abbreviated Magnetic Resonance Imaging (MRI) for Breast Cancer Screening: Rationale, Concept, and Transfer to Clinical Practice. *Annual Review of Medicine*, *70*(1), 501–519. https://doi.org/10.1146/annurev-med-121417-100403

Kuhl, C. K., Schrading, S., Strobel, K., Schild, H. H., Hilgers, R.-D., & Bieling, H. B. (2014). Abbreviated Breast Magnetic Resonance Imaging (MRI): First Postcontrast Subtracted Images and Maximum-Intensity Projection—A Novel Approach to Breast Cancer Screening With MRI. *JOURNAL OF CLINICAL ONCOLOGY*, 10.

Kuhl, C. K., Strobel, K., Bieling, H., Leutner, C., Schild, H. H., & Schrading, S. (2017). Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. *Radiology*, *283*(2), 361–370. https://doi.org/10.1148/radiol.2016161444

Kuhl, C., Weigel, S., Schrading, S., Arand, B., Bieling, H., König, R., Tombach, B., Leutner, C., Rieber-Brambs, A., Nordhoff, D., Heindel, W., Reiser, M., & Schild, H. H. (2010). Prospective Multicenter Cohort Study to Refine Management

Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial. *Journal of Clinical Oncology*, *28*(9), 1450–1457. https://doi.org/10.1200/JCO.2009.23.0839

Kumar, R., & Indrayan, A. (2011). Receiver operating characteristic (ROC) curve for medical researchers. *Indian Pediatrics*, *48*(4), 277–287. https://doi.org/10.1007/s13312-011-0055-4

Kwon, M., Choi, J. S., Won, H., Ko, E. Y., Ko, E. S., Park, K. W., & Han, B.-K. (2021). Breast Cancer Screening with Abbreviated Breast MRI: 3-year Outcome Analysis. *Radiology*, *299*(1), 73–83. https://doi.org/10.1148/radiol.2021202927

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Benbrahim-Tallaa, L., Bouvard, V., Bianchini, F., Straif, K., & International Agency for Research on Cancer Handbook Working Group (2015). Breast-cancer screening--viewpoint of the IARC Working Group. The New England journal of medicine, 372(24), 2353–2358. https://doi.org/10.1056/NEJMsr1504363

Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, Gilbert FJ, Griebsch I, Hoff RJ, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Thompson D, Warren RM, group Ms. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005; 365: 1769-1778. (PMID: 15910949) [CrossRef]

Lee, C. H., Bryce, Y., Zheng, J., Sung, J. S., Comstock, C. E., Moskowitz, C., & A. Morris, E. (2020). Outcome of Screening MRI in Premenopausal Women as a Function of the Week of the Menstrual Cycle. *American Journal of Roentgenology*, *214*(5), 1175–1181. https://doi.org/10.2214/AJR.18.19960

Lee, C. S., Monticciolo, D. L., & Moy, L. (2020). Screening Guidelines Update for Average-Risk and High-Risk Women. *American Journal of Roentgenology*, *214*(2), 316–323. https://doi.org/10.2214/AJR.19.22205

Lee, J. (2017). Practical and illustrated summary of updated BI-RADS for ultrasonography. *Ultrasonography*, *36*(1), 71–81. https://doi.org/10.14366/usg.16034

Lee-Felker, S., Joines, M., Storer, L., Li, B., DeBruhl, N., Sayre, J., & Hoyt, A. (2020). Abbreviated Breast MRI for Estimating Extent of Disease in Newly Diagnosed Breast Cancer. *Journal of Breast Imaging*, *2*(1), 43–49. https://doi.org/10.1093/jbi/wbz071

Lehman, C. D. (2006). Role of MRI in screening women at high risk for breast cancer. *Journal of Magnetic Resonance Imaging*, *24*(5), 964–970. https://doi.org/10.1002/jmri.20752

Lehman, C. D., Arao, R. F., Sprague, B. L., Lee, J. M., Buist, D. S. M., Kerlikowske, K., Henderson, L. M., Onega, T., Tosteson, A. N. A., Rauscher, G. H., & Miglioretti, D. L. (2017). National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. *Radiology*, *283*(1), 49–58. https://doi.org/10.1148/radiol.2016161174

Lehman, C. D., Lee, J. M., DeMartini, W. B., Hippe, D. S., Rendi, M. H., Kalish, G., Porter, P., Gralow, J., & Partridge, S. C. (2016). Screening MRI in Women With a Personal History of Breast Cancer. *Journal of the National Cancer Institute*, *108*(3), djv349. https://doi.org/10.1093/jnci/djv349

Leithner, D., Moy, L., Morris, E. A., Marino, M. A., Helbich, T. H., & Pinker, K. (2019). Abbreviated MRI of the Breast: Does It Provide Value? *Journal of Magnetic Resonance Imaging*, *49*(7), e85–e100. https://doi.org/10.1002/jmri.26291

Liao, Y.-S., Zhang, J.-Y., Hsu, Y.-C., Hong, M.-X., & Lee, L.-W. (2020). Age-Specific Breast Density Changes in Taiwanese Women: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health*, 13.

Liljequist, D., Elfving, B., & Skavberg Roaldsen, K. (2019). Intraclass correlation - A discussion and demonstration of basic features. PloS one, 14(7), e0219854. https://doi.org/10.1371/journal.pone.0219854

Liney, G. (2010). MRI from A to Z: A Definitive Guide for Medical Professionals. Springer London. https://books.google.com.mt/books?id=-_HVz-0HOlkC

Liu, L., Hao, X., Song, Z., Zhi, X., Zhang, S., & Zhang, J. (2021). Correlation between family history and characteristics of breast cancer. *Scientific Reports*, *11*(1), 6360. https://doi.org/10.1038/s41598-021-85899-8

Løberg, M., Lousdal, M. L., Bretthauer, M., & Kalager, M. (2015). Benefits and harms of mammography screening. Breast cancer research : BCR, 17(1), 63. https://doi.org/10.1186/s13058-015-0525-z

Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast Cancer—Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies—An Updated Review. *Cancers*, *13*(17), 4287. https://doi.org/10.3390/cancers1317428o7

Machida, Y., Shimauchi, A., Kanemaki, Y., Igarashi, T., Harada, M., & Fukuma, E. (2017). Feasibility and potential limitations of abbreviated breast MRI: An observer study using an enriched cohort. *Breast Cancer*, *24*(3), 411–419. https://doi.org/10.1007/s12282-016-0718-z

Malta National Cancer Registry, Directorate for Health Information and Research (2022)

Mandelson, M. T. (2000). Breast Density as a Predictor of Mammographic Detection: Comparison of Interval- and Screen-Detected Cancers. *Journal of the National Cancer Institute*, *92*(13), 1081–1087. https://doi.org/10.1093/jnci/92.13.1081

Mandrekar, J. N. (2010). Receiver Operating Characteristic Curve in Diagnostic Test Assessment. *Journal of Thoracic Oncology*, *5*(9), 1315–1316. https://doi.org/10.1097/JTO.0b013e3181ec173d

Mango, V. L., Goel, A., Mema, E., Kwak, E., & Ha, R. (2019). Breast MRI screening for average-risk women: A monte carlo simulation cost–benefit analysis. *Journal of Magnetic Resonance Imaging*, *49*(7), e216–e221. https://doi.org/10.1002/jmri.26334

Mango, V. L., Morris, E. A., David Dershaw, D., Abramson, A., Fry, C., Moskowitz, C. S., Hughes, M., Kaplan, J., & Jochelson, M. S. (2015). Abbreviated protocol for breast MRI: Are multiple sequences needed for cancer detection? *European Journal of Radiology*, *84*(1), 65–70. https://doi.org/10.1016/j.ejrad.2014.10.004

Mann, R. M., Athanasiou, A., Baltzer, P. A. T., Camps-Herrero, J., Clauser, P., Fallenberg, E. M., Forrai, G., Fuchsjäger, M. H., Helbich, T. H., Killburn-Toppin, F., Lesaru, M., Panizza, P., Pediconi, F., Pijnappel, R. M., Pinker, K., Sardanelli, F., Sella, T., Thomassin-Naggara, I., Zackrisson, S., … On behalf of the European Society of Breast Imaging (EUSOBI). (2022). Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI). *European Radiology*. https://doi.org/10.1007/s00330-022-08617-6

Mann, R. M., Balleyguier, C., Baltzer, P. A., Bick, U., Colin, C., Cornford, E., Evans, A., Fallenberg, E., Forrai, G., Fuchsjäger, M. H., Gilbert, F. J., Helbich, T. H., Heywang-Köbrunner, S. H., Camps-Herrero, J., Kuhl, C. K., Martincich, L., Pediconi, F., Panizza, P., Pina, L. J., Pijnappel, R. M., … European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer

Coalition (2015). Breast MRI: EUSOBI recommendations for women's information. European radiology, 25(12), 3669–3678. https://doi.org/10.1007/s00330-015-3807-z

Mann, R. M., Kuhl, C. K., & Moy, L. (2019). Contrast-enhanced MRI for breast cancer screening. *Journal of Magnetic Resonance Imaging*, *50*(2), 377–390. https://doi.org/10.1002/jmri.26654

Mann, R. M., Mus, R. D., van Zelst, J., Geppert, C., Karssemeijer, N., & Platel, B. (2014). A Novel Approach to Contrast-Enhanced Breast Magnetic Resonance Imaging for Screening: High-Resolution Ultrafast Dynamic Imaging. *Investigative Radiology*, *49*(9), 579–585. https://doi.org/10.1097/RLI.0000000000000057

Mann, R. M., van Zelst, J. C. M., Vreemann, S., & Mus, R. D. M. (2019). Is Ultrafast or Abbreviated Breast MRI Ready for Prime Time? *Current Breast Cancer Reports*, *11*(1), 9–16. https://doi.org/10.1007/s12609-019-0300-8

Mar, C., Sam, J., McGahan, C. E., DeVries, K., & Coldman, A. J. (2019). *The influence of breast density on breast cancer diagnosis: A study of participants in the BC Cancer Breast Screening Program*. 9.

Marino, M. A., Avendano, D., Zapata, P., Riedl, C. C., & Pinker, K. (2020). Lymph Node Imaging in Patients with Primary Breast Cancer: Concurrent Diagnostic Tools. *The Oncologist*, *25*(2), e231–e242. https://doi.org/10.1634/theoncologist.2019-0427

Marmot, M. G., Altman, D. G., Cameron, D. A., Dewar, J. A., Thompson, S. G., & Wilcox, M. (2013). The benefits and harms of breast cancer screening: An independent review: A report jointly commissioned by Cancer Research UK and the Department of Health (England) October 2012. *British Journal of Cancer*, *108*(11), 2205–2240. https://doi.org/10.1038/bjc.2013.177

Marquina Martínez, D., Cruz Ciria, S., García Barrado, A. I., Suñén Amador, I., & García Mur, C. (2020). Value of an abbreviated protocol of breast magnetic resonance imaging for screening high-risk patients. *Radiología (English Edition)*, *62*(3), 198–204. https://doi.org/10.1016/j.rxeng.2019.11.006

Marshall, H. N., & Plecha, D. M. (2020). Setting Up an Abbreviated Breast MRI Program: Our Two-year Implementation Experience. *Journal of Breast Imaging*, *2*(6), 603–608. https://doi.org/10.1093/jbi/wbaa060

Maxim, L. D., Niebo, R., & Utell, M. J. (2014). Screening tests: A review with examples. *Inhalation Toxicology*, *26*(13), 811–828. https://doi.org/10.3109/08958378.2014.955932

Maxwell, A. J., Ridley, N. T., Rubin, G., Wallis, M. G., Gilbert, F. J., & Michell, M. J. (2009). The Royal College of Radiologists Breast Group breast imaging classification. *Clinical Radiology*, *64*(6), 624–627. https://doi.org/10.1016/j.crad.2009.01.010

McDonald, E. S., Hammersley, J. A., Chou, S.-H. S., Rahbar, H., Scheel, J. R., Lee, C. I., Liu, C.-L., Lehman, C. D., & Partridge, S. C. (2016). Performance of DWI as a Rapid Unenhanced Technique for Detecting Mammographically Occult Breast Cancer in Elevated-Risk Women With Dense Breasts. *American Journal of Roentgenology*, *207*(1), 205–216. https://doi.org/10.2214/AJR.15.15873

McHugh M. L. (2012). Interrater reliability: the kappa statistic. *Biochemia medica*, *22*(3), 276–282.

Mcleod, S. (2017). Qualitative vs Quantitative Research | Simply Psychology. Retrieved from https://www.simplypsychology.org/qualitative-quantitative.html

McJury, M. J. (2022). Acoustic Noise and Magnetic Resonance Imaging : A Narrative/Descriptive Review. *Journal of Magnetic Resonance Imaging*, *55*(2), 337–346. https://doi.org/10.1002/jmri.27525

Menezes, G. L. (2014). Magnetic resonance imaging in breast cancer: A literature review and future perspectives. *World Journal of Clinical Oncology*, *5*(2), 61. https://doi.org/10.5306/wjco.v5.i2.61

Ministry of Health. (2017) The National Cancer Plan for the Maltese Islands.

Modi, S., Saura, C., Yamashita, T., Park, Y. H., Kim, S.-B., Tamura, K., Andre, F., Iwata, H., Ito, Y., Tsurutani, J., Sohn, J., Denduluri, N., Perrin, C., Aogi, K., Tokunaga, E., Im, S.-A., Lee, K. S., Hurvitz, S. A., Cortes, J., … Krop, I. (2020). Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *New England Journal of Medicine*, *382*(7), 610–621. https://doi.org/10.1056/NEJMoa1914510

Momenimovahed, Z., & Salehiniya, H. (2019). Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer: Targets and Therapy*, *Volume 11*, 151–164. https://doi.org/10.2147/BCTT.S176070

Monticciolo, D. L., Malak, S. F., Friedewald, S. M., Eby, P. R., Newell, M. S., Moy, L., Destounis, S., Leung, J. W. T., Hendrick, R. E., & Smetherman, D. (2021). Breast Cancer Screening Recommendations Inclusive of All Women at Average Risk: Update from the ACR and Society of Breast Imaging. *Journal of the American College of Radiology*, *18*(9), 1280–1288. https://doi.org/10.1016/j.jacr.2021.04.021

Monticciolo, D. L., Newell, M. S., Moy, L., Niell, B., Monsees, B., & Sickles, E. A. (2018). Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. *Journal of the American College of Radiology*, *15*(3), 408–414. https://doi.org/10.1016/j.jacr.2017.11.034

Mootz, A. R., Madhuranthakam, A. J., Department of Radiology, University of Texas Southwestern Medical School, Texas, USA, Dogan, B., & Department of Radiology, University of Texas Southwestern Medical School, Texas, USA. (2019). Changing Paradigms in Breast Cancer Screening: Abbreviated Breast MRI. *European Journal of Breast Health*, *15*(1), 1–6. https://doi.org/10.5152/ejbh.2018.4402

Morris EA, Comstock CE, Lee CH, et al. ACR BI-RADS® Magnetic Resonance Imaging. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

Morris, E. A. (2014). Rethinking Breast Cancer Screening: Ultra FAST Breast Magnetic Resonance Imaging. *Journal of Clinical Oncology*, *32*(22), 2281–2283. https://doi.org/10.1200/JCO.2014.56.1514

Morris, E. A., Liberman, L., Ballon, D. J., Robson, M., Abramson, A. F., Heerdt, A., & Dershaw, D. D. (2003). *MRI of Occult Breast Carcinoma in a High-Risk Population*. 8.

Moschetta, M., Telegrafo, M., Rella, L., Stabile Ianora, A. A., & Angelelli, G. (2016). Abbreviated Combined MR Protocol: A New Faster Strategy for Characterizing Breast Lesions. *Clinical Breast Cancer*, *16*(3), 207–211. https://doi.org/10.1016/j.clbc.2016.02.008

Mussetto, I., Gristina, L., Schiaffino, S., Tosto, S., Raviola, E., & Calabrese, M. (2020). Breast ultrasound: Automated or hand-held? Exploring patients' experience and preference. *European Radiology Experimental*, *4*(1), 12. https://doi.org/10.1186/s41747-019-0136-z

Nalawade, Y. V. (2009). *Evaluation of breast calcifications*. *19*(4), 6.

National Comprehensive Cancer Network (NCCN). (2016). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 2.2016).

Nounou, M. I., ElAmrawy, F., Ahmed, N., Abdelraouf, K., Goda, S., & Syed-Sha-Qhattal, H. (2015). Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. *Breast Cancer: Basic and Clinical Research*, *9s2*, BCBCR.S29420. https://doi.org/10.4137/BCBCR.S29420

Oldrini, G., Derraz, I., Salleron, J., Marchal, F., & Henrot, P. (2018). Impact of an abbreviated protocol for breast MRI in diagnostic accuracy. *Diagnostic and Interventional Radiology*, *24*(1), 12–16. https://doi.org/10.5152/dir.2018.16609

Oldrini, G., Fedida, B., Poujol, J., Felblinger, J., Trop, I., Henrot, P., Darai, E., & Thomassin-Naggara, I. (2017). Abbreviated breast magnetic resonance protocol: Value of high-resolution temporal dynamic sequence to improve lesion characterization. *European Journal of Radiology*, *95*, 177–185. https://doi.org/10.1016/j.ejrad.2017.07.025

Ozhan Caparlar, C., & Donmez, A. (2016). What is Scientific Research and How Can it be Done? *Turkish Journal of Anesthesia and Reanimation*, *44*(4), 212–218. https://doi.org/10.5152/TJAR.2016.34711

Pacilè, S., Lopez, J., Chone, P., Bertinotti, T., Grouin, J. M., & Fillard, P. (2020). Improving Breast Cancer Detection Accuracy of Mammography with the Concurrent Use of an Artificial Intelligence Tool. *Radiology: Artificial Intelligence*, *2*(6), e190208. https://doi.org/10.1148/ryai.2020190208

Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M. J., Gilbert, F., & Senkus, E. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Annals of Oncology*, *27*, v103–v110. https://doi.org/10.1093/annonc/mdw327

Panigrahi, B., Mullen, L., Falomo, E., Panigrahi, B., & Harvey, S. (2017). An Abbreviated Protocol for High-risk Screening Breast Magnetic Resonance Imaging. *Academic Radiology*, *24*(9), 1132–1138. https://doi.org/10.1016/j.acra.2017.03.014

Parikh, R., Mathai, A., Parikh, S., Sekhar, G. C., & Thomas, R. (2008). Understanding and using sensitivity, speciÞcity and predictive values. *Indian Journal of Ophthalmology*, *56*(1), 6.

Pediconi, F., Catalano, C., Roselli, A., Dominelli, V., Cagioli, S., Karatasiou, A., Pronio, A., Kirchin, M. A., & Passariello, R. (2009). The Challenge of Imaging Dense Breast Parenchyma: Is Magnetic Resonance Mammography the Technique of Choice? A Comparative Study With X-Ray Mammography and Whole-Breast Ultrasound. *Investigative Radiology*, *44*(7), 412–421. https://doi.org/10.1097/RLI.0b013e3181a53654

Petrillo, A., Fusco, R., Sansone, M., Cerbone, M., Filice, S., Porto, A., Rubulotta, M. R., D'Aiuto, M., Avino, F., Di Bonito, M., & Botti, G. (2017). Abbreviated breast dynamic contrast-enhanced MR imaging for lesion detection and characterization: The experience of an Italian oncologic center. *Breast Cancer Research and Treatment*, *164*(2), 401–410. https://doi.org/10.1007/s10549-017-4264-y

Pham, R., Marshall, H., & Plecha, D. (2020). Abbreviated Protocol Breast MRI. *American Journal of Roentgenology*, *215*(3), 765–769. https://doi.org/10.2214/AJR.19.22292

Phi, X.-A., Tagliafico, A., Houssami, N., Greuter, M. J. W., & de Bock, G. H. (2018). Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts – a systematic review and meta-analysis. *BMC Cancer*, *18*(1), 380. https://doi.org/10.1186/s12885-018-4263-3

Pineda, F. D., Medved, M., Wang, S., Fan, X., Schacht, D. V., Sennett, C., Oto, A., Newstead, G. M., Abe, H., & Karczmar, G. S. (2016). Ultrafast Bilateral DCE-MRI

of the Breast with Conventional Fourier Sampling. *Academic Radiology*, *23*(9), 1137–1144. https://doi.org/10.1016/j.acra.2016.04.008

Pinker, K., Moy, L., Sutton, E. J., Mann, R. M., Weber, M., Thakur, S. B., Jochelson, M. S., Bago-Horvath, Z., Morris, E. A., Baltzer, P. A., & Helbich, T. H. (2018). Diffusion-Weighted Imaging With Apparent Diffusion Coefficient Mapping for Breast Cancer Detection as a Stand-Alone Parameter: Comparison With Dynamic Contrast-Enhanced and Multiparametric Magnetic Resonance Imaging. *Investigative Radiology*, *53*(10), 587–595. https://doi.org/10.1097/RLI.0000000000000465

Pinsky, R. W., & Helvie, M. A. (2010). Mammographic Breast Density: Effect on Imaging and Breast Cancer Risk. *Journal of the National Comprehensive Cancer Network*, *8*(10), 1157–1165. https://doi.org/10.6004/jnccn.2010.0085

Podo, Franca & Sardanelli, Francesco & Canese, Rossella & D'Agnolo, G & Natali, P & Crecco, M & Grandinetti, Lucio & Musumeci, R & Trecate, Giovanna & Bergonzi, S & Simone, T & Costa, C & Pasini, Barbara & Manoukian, Siranoush & Spatti, Gianbattista & Vergnaghi, Daniele & Morassut, S & Boiocchi, M & Dolcetti, Riccardo & Maschio, A. (2002). The Italian multi-centre project on evaluation of MRI and other imaging modalities in early detection of breast cancer in subjects at high genetic risk. Journal of experimental & clinical cancer research : CR. 21. 115-24.

Polit, D., & Beck, C. (2010). Essentials of nursing research. (7th Edition) Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Polit, D. F., & Beck, C. T. (2014). *Essentials of nursing research: appraising evidence for nursing practice.* 8th ed. Philadelphia: Wolters Kluwer Health /Lippincott Williams & Wilkins.

Polit, D. F., & Beck, C. T. (2017). *Nursing Research: Generating and Assessing Evidence for Nursing Practice* (10th ed.). Wolters Kluwer.

Polit, D. F., & Beck, C. T. (2018). *Essentials of nursing research: Appraising evidence for nursing practice* (Ninth edition). Wolters Kluwer Health.

Polit, D. F., & Beck, C. T. (2018). *Essentials of nursing research: Appraising evidence for nursing practice* (10th ed). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Polit, D. F., & Beck, C. T. (2020). Nursing research: generating and assessing evidence for nursing practice. Eleventh edition. Philadelphia, Wolters Kluwer.

Punglia, R. S., & Hassett, M. J. (2010). Using Lifetime Risk Estimates to Recommend Magnetic Resonance Imaging Screening for Breast Cancer Survivors. *Journal of Clinical Oncology*, *28*(27), 4108–4110. https://doi.org/10.1200/JCO.2010.30.0350

Ramalho, J., Semelka, R. C., Ramalho, M., Nunes, R. H., AlObaidy, M., & Castillo, M. (2016). Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update. *American Journal of Neuroradiology*, *37*(7), 1192–1198. https://doi.org/10.3174/ajnr.A4615

Ranganathan, P., & Aggarwal, R. (2018). *Study designs: Part 1 – An overview and classification*. 3.

Rella, R., Belli, P., Giuliani, M., Bufi, E., Carlino, G., Rinaldi, P., & Manfredi, R. (2018). Automated Breast Ultrasonography (ABUS) in the Screening and Diagnostic Setting. *Academic Radiology*, *25*(11), 1457–1470. https://doi.org/10.1016/j.acra.2018.02.014

Reeves, R. A., & Kaufman, T. (2022). Mammography. In *StatPearls*. StatPearls Publishing.

Rice, M. S., Bertrand, K. A., VanderWeele, T. J., Rosner, B. A., Liao, X., Adami, H.-O., & Tamimi, R. M. (2016). Mammographic density and breast cancer risk: A mediation

analysis. *Breast Cancer Research, 18*(1), 94. https://doi.org/10.1186/s13058-016-0750-0

Riedl, C. C., Luft, N., Bernhart, C., Weber, M., Bernathova, M., Tea, M.-K. M., Rudas, M., Singer, C. F., & Helbich, T. H. (2015). Triple-Modality Screening Trial for Familial Breast Cancer Underlines the Importance of Magnetic Resonance Imaging and Questions the Role of Mammography and Ultrasound Regardless of Patient Mutation Status, Age, and Breast Density. *Journal of Clinical Oncology*, *33*(10), 1128–1135. https://doi.org/10.1200/JCO.2014.56.8626

Roca, S. A., Delgado Laguna, A. B., Arantzeta Lexarreta, J., Cajal Campo, B., & Santamaría Jareño, S. (2020). Screening in patients with increased risk of breast cancer (part 1): Pros and cons of MRI screening. *Radiología (English Edition)*, *62*(4), 252–265. https://doi.org/10.1016/j.rxeng.2020.01.009

Roganovic, D., Djilas, D., Vujnovic, S., Pavic, D., & Stojanov, D. (2015). Breast MRI, digital mammography and breast tomosynthesis: Comparison of three methods for early detection of breast cancer. *Bosnian Journal of Basic Medical Sciences*, *15*(4). https://doi.org/10.17305/bjbms.2015.616

Romeo, V., Cuocolo, R., Liuzzi, R., Riccardi, A., Accurso, A., Acquaviva, A., Buonocore, R., & Imbriaco, M. (2017). Preliminary Results of a Simplified Breast MRI Protocol to Characterize Breast Lesions. *Academic Radiology*, *24*(11), 1387–1394. https://doi.org/10.1016/j.acra.2017.04.011

Saadatmand, S., Geuzinge, H. A., Rutgers, E. J. T., Mann, R. M., de Roy van Zuidewijn, D. B. W., Zonderland, H. M., Tollenaar, R. A. E. M., Lobbes, M. B. I., Ausems, M. G. E. M., van ’t Riet, M., Hooning, M. J., Mares-Engelberts, I., Luiten, E. J. T., Heijnsdijk, E. A. M., Verhoef, C., Karssemeijer, N., Oosterwijk, J. C., Obdeijn, I.-M., de Koning, H. J., … van Druten, E. (2019). MRI versus mammography for breast

cancer screening in women with familial risk (FaMRIsc): A multicentre, randomised, controlled trial. *The Lancet Oncology*, *20*(8), 1136–1147. https://doi.org/10.1016/S1470-2045(19)30275-X

Safari, S., Baratloo, A., Elfil, M., & Negida, A. (2015). *Evidence Based Emergency Medicine Part 2: Positive and negative predictive values of diagnostic tests*. 2.

Sardanelli, F., Aase, H. S., Álvarez, M., Azavedo, E., Baarslag, H. J., Balleyguier, C., Baltzer, P. A., Beslagic, V., Bick, U., Bogdanovic-Stojanovic, D., Briediene, R., Brkljacic, B., Camps Herrero, J., Colin, C., Cornford, E., Danes, J., de Geer, G., Esen, G., Evans, A., … Forrai, G. (2017). Position paper on screening for breast cancer by the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies from Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Israel, Lithuania, Moldova, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland and Turkey. *European Radiology*, *27*(7), 2737–2743. https://doi.org/10.1007/s00330-016-4612-z

Sardanelli, F., & Podo, F. (2007). Breast MR imaging in women at high-risk of breast cancer. Is something changing in early breast cancer detection? *European Radiology*, *17*(4), 873–887. https://doi.org/10.1007/s00330-006-0389-9

Salem, D. S., Kamal, R. M., Mansour, S. M., Salah, L. A., & Wessam, R. (2013). Breast imaging in the young: the role of magnetic resonance imaging in breast cancer screening, diagnosis and follow-up. Journal of thoracic disease, 5 Suppl 1(Suppl 1), S9–S18. https://doi.org/10.3978/j.issn.2072-1439.2013.05.02

Saslow, D., Boetes, C., Burke, W., Harms, S., Leach, M. O., Lehman, C. D., Morris, E., Pisano, E., Schnall, M., Sener, S., Smith, R. A., Warner, E., Yaffe, M., Andrews, K. S., Russell, C. A., & for the American Cancer Society Breast Cancer Advisory

Group. (2007). American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. *CA: A Cancer Journal for Clinicians*, *57*(2), 75–89. https://doi.org/10.3322/canjclin.57.2.75

Seely, J. M. (2017). How Effective Is Mammography as a Screening Tool? *Current Breast Cancer Reports*, *9*(4), 251–258. https://doi.org/10.1007/s12609-017-0257-4

Shahid, H., Wiedenhoefer, J. F., Dornbluth, C., Otto, P., & Kist, K. A. (2016). An overview of breast MRI. *Applied Radiology*, 7–13. https://doi.org/10.37549/AR2317

Sharma, G. N., Dave, R., Sanadya, J., Sharma, P., & Sharma, K. K. (2010). Various types and management of breast cancer: an overview. *Journal of advanced pharmaceutical technology & research*, *1*(2), 109–126.

Shen, Y., Winget, M., & Yuan, Y. (2017). The impact of false positive breast cancer screening mammograms on screening retention: A retrospective population cohort study in Alberta, Canada. *Canadian Journal of Public Health*, *108*(5–6), e539–e545. https://doi.org/10.17269/CJPH.108.6154

Shin, H. J., Chae, E. Y., Choi, W. J., Ha, S. M., Park, J. Y., Shin, K. C., Cha, J. H., & Kim, H. H. (2016). Diagnostic Performance of Fused Diffusion-Weighted Imaging Using Unenhanced or Postcontrast T1-Weighted MR Imaging in Patients With Breast Cancer. *Medicine*, *95*(17), e3502. https://doi.org/10.1097/MD.0000000000003502

Shiovitz, S., & Korde, L. A. (2015). Genetics of breast cancer: A topic in evolution. *Annals of Oncology*, *26*(7), 1291–1299. https://doi.org/10.1093/annonc/mdv022

Shreffler, J., & Huecker, M. R. (2022). Type I and Type II Errors and Statistical Power. In *StatPearls*. StatPearls Publishing.

Siu, A. L. (2016). *Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement*. 19.

Strahle, D. A., Pathak, D. R., Sierra, A., Saha, S., Strahle, C., & Devisetty, K. (2017). Systematic development of an abbreviated protocol for screening breast magnetic resonance imaging. *Breast Cancer Research and Treatment*, *162*(2), 283–295. https://doi.org/10.1007/s10549-017-4112-0

Strigel, R. M., Burnside, E. S., Elezaby, M., Fowler, A. M., Kelcz, F., Salkowski, L. R., & DeMartini, W. B. (2017). Utility of BI-RADS Assessment Category 4 Subdivisions for Screening Breast MRI. *American Journal of Roentgenology*, *208*(6), 1392–1399. https://doi.org/10.2214/AJR.16.16730

Sun, Y.-S., Zhao, Z., Yang, Z.-N., Xu, F., Lu, H.-J., Zhu, Z.-Y., Shi, W., Jiang, J., Yao, P.-P., & Zhu, H.-P. (2017). Risk Factors and Preventions of Breast Cancer. *International Journal of Biological Sciences*, *13*(11), 1387–1397. https://doi.org/10.7150/ijbs.21635

Sung, J. S., Lebron, L., Keating, D., D'Alessio, D., Comstock, C. E., Lee, C. H., Pike, M. C., Ayhan, M., Moskowitz, C. S., Morris, E. A., & Jochelson, M. S. (2019). Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer. *Radiology*, *293*(1), 81–88. https://doi.org/10.1148/radiol.2019182660

Sung, J. S., Stamler, S., Brooks, J., Kaplan, J., Huang, T., Dershaw, D. D., Lee, C. H., Morris, E. A., & Comstock, C. E. (2016). Breast Cancers Detected at Screening MR Imaging and Mammography in Patients at High Risk: Method of Detection Reflects Tumor Histopathologic Results. *Radiology*, *280*(3), 716–722. https://doi.org/10.1148/radiol.2016151419

Sutton, J., & Austin, Z. (2015). Qualitative Research: Data Collection, Analysis, and Management. The Canadian Journal of Hospital Pharmacy, 68(3). https://doi.org/10.4212/cjhp.v68i3.1456

Tabar, L., Yen, M.-F., Vitak, B., Chen, H.-H. T., Smith, R. A., & Duffy, S. W. (2003). Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *The Lancet*, *361*(9367), 1405–1410. https://doi.org/10.1016/S0140-6736(03)13143-1

Tabár, L., Yen, A. M., Wu, W. Y., Chen, S. L., Chiu, S. Y., Fann, J. C., Ku, M. M., Smith, R. A., Duffy, S. W., & Chen, T. H. (2015). Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. The breast journal, 21(1), 13–20. https://doi.org/10.1111/tbj.12354

Taneja, C., Edelsberg, J., Weycker, D., Guo, A., Oster, G., & Weinreb, J. (2009). Cost Effectiveness of Breast Cancer Screening With Contrast-Enhanced MRI in High-Risk Women. *Journal of the American College of Radiology*, *6*(3), 171–179. https://doi.org/10.1016/j.jacr.2008.10.003

Taylor, K., Britton, P., O'Keeffe, S., & Wallis, M. G. (2011). Quantification of the UK 5-point breast imaging classification and mapping to BI-RADS to facilitate comparison with international literature. *The British Journal of Radiology*, *84*(1007), 1005–1010. https://doi.org/10.1259/bjr/48490964

Tenny, S., Brannan GD., Brannan, JM., Sharts-Hopko, NC. (2020) Qualitative Study. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing Retrieved June 12, 2021 from https://www.ncbi.nlm.nih.gov/books/NBK470395/

The American College of Obstetrics and Gynecology (2017). Breast Cancer Risk Assessment and Screening in Average-Risk Women, Obstetrics & Gynecology. ACOG Practice Bulletin No. 179 Summary, 130(1), 241-243. doi: 10.1097/AOG.0000000000002151

The American Society of Breast Surgeons (2019). Position statement on screening mammography. Retrieved on April 25th, 2022, from https://www.breastsurgeons.org/docs/statements/ Position-Statement-on-Screening-Mammography."

Théberge, I., Vandal, N., Langlois, A., Pelletier, É., & Brisson, J. (2016). Detection Rate, Recall Rate, and Positive Predictive Value of Digital Compared to Screen-Film Mammography in the Quebec Population-Based Breast Cancer Screening Program. Canadian Association of Radiologists Journal, 67(4), 330–338.doi:10.1016/j.carj.2016.02.001

Thewes, B., Rietjens, J. A. C., van den Berg, S. W., Compen, F. R., Abrahams, H., Poort, H., van de Wal, M., Schellekens, M. P. J., Peters, M. E. W. J., Speckens, A. E. M., Knoop, H., & Prins, J. B. (2018). One way or another: The opportunities and pitfalls of self-referral and consecutive sampling as recruitment strategies for psycho-oncology intervention trials. *Psycho-Oncology*, *27*(8), 2056–2059. https://doi.org/10.1002/pon.4780

Tosteson, A. N. A., Fryback, D. G., Hammond, C. S., Hanna, L. G., Grove, M. R., Brown, M., Wang, Q., Lindfors, K., & Pisano, E. D. (2014). Consequences of False-Positive Screening Mammograms. *JAMA Internal Medicine*, *174*(6), 954. https://doi.org/10.1001/jamainternmed.2014.981

Trecate, G., Vergnaghi, D., Manoukian, S., Bergonzi, S., Scaperrotta, G., Marchesini, M., Ferranti, C., Peissel, B., Spatti, G., Bohm, S., Conti, A., Costa, C., Sporeni, M., Podo, F., & Musumeci, R. (2006). MRI in the Early Detection of Breast Cancer in Women with High Genetic Risk. *Tumori Journal*, *92*(6), 517–523. https://doi.org/10.1177/030089160609200609

Trochim, W., Donnelly, J., & Arora, K. (2016). Research Methods: The Essential Knowledge Base.

Trevethan, R. (2017). Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Frontiers in Public Health*, *5*, 307. https://doi.org/10.3389/fpubh.2017.00307

Vegunta, S., Bhatt, A. A., Choudhery, S. A., Pruthi, S., & Kaur, A. S. (2021). Identifying women with increased risk of breast cancer and implementing risk-reducing strategies and supplemental imaging. *Breast Cancer*, *29*(1), 19–29. https://doi.org/10.1007/s12282-021-01298-x

Vinnicombe, S., Harvey, H., Healy, N. A., Papalouka, V., Schiller, A., Moyle, P., Kilburn-Toppin, F., Allajbeu, I., Sharma, N., Maxwell, A. J., Payne, N., Graves, M., & Gilbert, F. J. (2021). Introduction of an abbreviated breast MRI service in the UK as part of the BRAID trial: Practicalities, challenges, and future directions. *Clinical Radiology*, *76*(6), 427–433. https://doi.org/10.1016/j.crad.2021.01.020

Waltz, C. F., Strickland, O. L., & Lenz, E. R. (2010*). Measurement in nursing and health research* (4th ed.). Springer Publishing Company.

Wanders, J. O. P., van Gils, C. H., Karssemeijer, N., Holland, K., Kallenberg, M., Peeters, P. H. M., Nielsen, M., & Lillholm, M. (2018). The combined effect of mammographic texture and density on breast cancer risk: A cohort study. *Breast Cancer Research*, *20*(1), 36. https://doi.org/10.1186/s13058-018-0961-7

Wang, Y., Chen, H., Li, N., Ren, J., Zhang, K., Dai, M., & He, J. (2019). Ultrasound for Breast Cancer Screening in High-Risk Women: Results From a Population-Based Cancer Screening Program in China. *Frontiers in Oncology*, *9*, 286. https://doi.org/10.3389/fonc.2019.00286

Warner, E., Plewes, D. B., Hill, K. A., Causer, P. A., Zubovits, J. T., Jong, R. A., Cutrara, M. R., DeBoer, G., Yaffe, M. J., Messner, S. J., Meschino, W. S., Piron, C. A., & Narod, S. A. (2004). *Surveillance of BRCA1 and BRCA2 Mutation Carriers With Magnetic Resonance Imaging, Ultrasound, Mammography, and Clinical Breast Examination*. 9.

Warrier, S., Tapia, G., Goltsman, D., & Beith, J. (2016). An Update in Breast Cancer Screening and Management. *Women's Health*, *12*(2), 229–239. https://doi.org/10.2217/whe.15.105

Watson R. Quantitative research. Nurs Stand. 2015 Apr 1;29(31):44-8. doi: 10.7748/ns.29.31.44.e8681. PMID: 25828021.

Webb, M. L., Cady, B., Michaelson, J. S., Bush, D. M., Calvillo, K. Z., Kopans, D. B., & Smith, B. L. (2014). A failure analysis of invasive breast cancer: Most deaths from disease occur in women not regularly screened: Most Breast Cancer Deaths Not Screened. *Cancer*, *120*(18), 2839–2846. https://doi.org/10.1002/cncr.28199

Weigel, S., Heindel, W., Heidrich, J., Hense, H.-W., & Heidinger, O. (2016). Digital mammography screening: Sensitivity of the programme dependent on breast density. *European Radiology*, *27*(7), 2744–2751. https://doi.org/10.1007/s00330-016-4636-4

Welch, H. G., Prorok, P. C., O'Malley, A. J., & Kramer, B. S. (2016). Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness. *New England Journal of Medicine*, *375*(15), 1438–1447. https://doi.org/10.1056/NEJMoa1600249

Wen, H. Y., & Brogi, E. (2018). Lobular Carcinoma In Situ. *Surgical Pathology Clinics*, *11*(1), 123–145. https://doi.org/10.1016/j.path.2017.09.009

Wohlin, C. (2014). Guidelines for Snowballing in Systematic Literature Studies and a Replication in Software Engineering. Evaluation and Assessment in Software Engineering – EASE.

World Health Organization. (2021, March 26th). "Breast Cancer" Retrieved March 18th 2023, from https://www.who.int/news-room/fact-sheets/detail/breast-cancer

World Health Organization. (2022, February 3rd). "Cancer" Retrieved March 18th 2023, from https://www.who.int/news-room/fact-sheets/detail/cancer

Yaghjyan, L., Colditz, G. A., Collins, L. C., Schnitt, S. J., Rosner, B., Vachon, C., & Tamimi, R. M. (2011). Mammographic Breast Density and Subsequent Risk of Breast Cancer in Postmenopausal Women According to Tumor Characteristics. *JNCI Journal of the National Cancer Institute*, *103*(15), 1179–1189. https://doi.org/10.1093/jnci/djr225

Yankaskas, B. C., Cleveland, R. J., Schell, M. J., & Kozar, R. (2001). Association of Recall Rates with Sensitivity and Positive Predictive Values of Screening Mammography. *American Journal of Roentgenology*, *177*(3), 543–549. https://doi.org/10.2214/ajr.177.3.1770543

Zamanzadeh, V., Ghahramanian, A., Rassouli, M., Abbaszadeh, A., Alavi-Majd, H., & Nikanfar, A.-R. (2015). Design and Implementation Content Validity Study: Development of an instrument for measuring Patient-Centered Communication. *Journal of Caring Sciences*, *4*(2), 165–178. https://doi.org/10.15171/jcs.2015.017

Zendehdel, M., Niakan, B., Keshtkar, A., Rafiei, E., & Salamat, F. (2018). Subtypes of Benign Breast Disease as a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis Protocol. Iranian journal of medical sciences, 43(1), 1–8.

Zou, K. H., O'Malley, A. J., & Mauri, L. (2007). Receiver-Operating Characteristic Analysis for Evaluating Diagnostic Tests and Predictive Models. *Circulation*, *115*(5), 654–657. https://doi.org/10.1161/CIRCULATIONAHA.105.594929

Appendices

Appendix A1

Letters of Approval and Permissions

Dr. Kenneth Saliba
Chairperson
Medical Imaging Department

L-Università ta' Malta

22/11/2021

Dear Dr. Saliba

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes.

The target population will be patients who performed a breast MRI examination. Whilst the accessible population will include patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this is is when the most recent exams were performed using the updated full protocol on a 3-T Philips unit. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

A minimum of two radiologists specialised in breast imaging with a minimum of two years of experience in MRI breast reporting will be conveniently selected to evaluate the diagnostic accuracy of an abbreviated protocol when compared to the full protocol. The abbreviated protcol will be presented to the radiologists who will review the images and fill in the data collection tool for each set of images. The data collected from the abbreviated protocol will be compared with the data from the report issued from the MRI using the full protocol. Lesions with a final BI-RADS category of 1 or 2 will be considered as **negative** findings while those with a final BI-RADS of 3,4 or 5 will be considered **positive** findings. The findings will then be compared with the gold standard being the histo-pathological correlation of a breast lesion or at least 12 months of negative findings on follow-up imaging with either mammography, ultrasound or MRI in the absence of a biopsy.

In line with ethical requirements, I would like to ask for your permission:

- So that the radiographer acting as the intermediary person to access the picture archiving and communication system (PACS) and iSoft archive to identify the required MR cases for the purpose of this study.
- For the intermediary person/s to contact the patient participants who are randomly selected, to obtain their informed consent to use their MR images, imaging reports and histo-pathological findings for the purpose of the study. For the intermediary person/s to retrieve their MR images and anonymise them to be used for the study.
- For the intermediary person/s to invite radiologists to participate in the image pathology identification and supply them with the anonymised images for image pathology identification.

Kindly note that permission and approval to conduct this study will be sought from the Faculty of Health Sciences Research and Ethics Committee (FREC) and University Research Ethics Committee (UREC DP). Permission from the Hospital chief executive officer (CEO) and Data Protection Officer (DPO) are also going to be obtained. I can assure you that all ethical issues would be considered throughout the study and addressed.

If you are in agreement, I kindly ask you to complete and sign this letter. Should you wish any further information or clarification about the proposed study, please contact me on +356 [redacted] or my supervisors; Dr. Francis Zarb [redacted] Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted]

I Thank you in advance,

Kind Regards,

Leanne Galea

[redacted]

Leanne Galea
Researcher

Comments:
Provided all related activity is conducted outside individual's working hours & that such related does not impede or detract from normal workflow.

Dr. Kenneth Saliba
Chairperson Medical Imaging Department

Signature: [redacted]

Approval: Granted / ~~Not Granted~~

Date: 22/11/2021

Mr Raymond Spiteri
Radiography Lead
Medical Imaging Department

L-Università ta' Malta

22/11/2021

Dear Mr. Spiteri

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes.

The target population will be patients who performed a breast MRI examination. Whilst the accessible population will include patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this is is when the most recent exams were performed using the updated full protocol on a 3-T Philips unit. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

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- For the intermediary person/s to retrieve their MR images and anonymise them to be used for the study.
- For the intermediary person/s to invite radiologists to participate in the image pathology identification and supply them with the anonymised images for image pathology identification.

Kindly note that permission and approval to conduct this study will be sought from the Faculty of Health Sciences (FREC) and University Research Ethics Committee (UREC DP). Permission from the Hospital CEO and Data Protection Officer are also going to be obtained. I can assure you that all ethical issues would be considered throughout the study and addressed.

If you are in agreement, kindly complete and sign this letter. Should you wish any further information or clarification about the proposed study, please contact me on +356 by e-mail or my supervisors; . Dr. Paul Bezzina (and Ms Deborah Mizzi

I Thank you in advance,

Kind Regards,

Leanne Galea
Researcher

breast Magnetic Resonance Imaging (MRI) protocol'

Comments:

Mr. Raymond Spiteri

Radiography Lead Medical Imaging Department Signature:

Approval: Granted / ~~Not Granted~~ Date: 22/11/2021

L-Università ta' Malta

Leanne Galea [redacted]

Seeking permission to perform Research Study

Leanne Galea [redacted] 23 November 2021 at 15:25
To: [redacted]
Cc: [redacted]
<de[redacted]

To whom it may concern,

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

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The target population will be patients who performed a breast MRI examination. Whilst the accessible population will include patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this is when the most recent exams were performed using the updated full protocol on a 3-T Philips unit. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

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In line with ethical requirements, I would like to ask for your permission:

- So that I can identify and invite a radiographer to act as an intermediary person to access the picture archiving and communication system (PACS) and iSoft archive to identify

L-Università ta' Malta

[redacted]

Seeking permission to perform Research Study

Data Protection at Health-MDH [redacted]
To: Leanne Galea [redacted]
Cc: Young Sharon at Health-MDH [redacted] Francis Zarb

Dear Ms Galea

On the basis of the documentation you submitted, from the MDH data protection point of view you have been cleared to proceed with your study titled ***The impact on diagnostic accuracy of*** please provide the relevant documents including Dr Kenneth Saliba's approval and this email).

- Your intermediary to approach potential participant patients via postal services on your behalf is *Ms Tiziana Muscat - Allied Health Professional (Radiographer)*
- Your potential participants to consent you to access their medical images that were captured between January 2019- December 2021 are *Data Subjects over th* stored at MDH
- Your intermediaries to approach the two Radiologists who work at the Medical Imaging Department, MDH are, *Ms Tiziana Muscat - Allied Health Professional (R* Imaging Department, MDH
- Your potential participants to evaluate the medical images following patient consent are two Radiologists who work at the Medical Imaging Department, MDH (who are on MDH HR and

All data stored must be anonymized and in no way should you retain any personal details you obtain from your research and these should be destroyed at the end of your study and /or if an

Anonymisation and Data minimisation

Participant consent forms must be separated from any Health Data at source meaning that there will be no correlation between one and the other that will identify your participant.

ALL data presented to your supervisors / tutors or examiners or any other personnel from UOM or anyone else must be already anonymized, meaning that you must not divulge to anyon

- If any patient wants to enquire who may have accessed personal data for verification purposes (in exceptional circumstances) from UOM and to enquire who were the two MDH Radiolo contact details that you included with the consent documents.
- If the two Radiologists want to enquire who accessed their personal data for verification purposes (in exceptional circumstances) from UOM, they may contact Dr Paul Bezzina, Dr Fran

Consent Criteria

This clearance allows viewing of medical images only after you have obtained explicit written consent by the data subjects.

Medical images or parts of cannot be published anywhere.

The two selected Radiologists must be MDH employees.

Data from MDH Health Information Systems may only be accessed by your intermediaries.

Potential patients must be reached and approached by Ms Tiziana Muscat via postal services and not via email, telephone, when physically at MDH grounds or any other means. You cannot b

The two Radiologists must be reached and approached by Ms Tiziana Muscat, Mr Claude Portanier Mifsud and Ms Marion Borg when physically at MDH grounds and not via postal services vi

Personal identifiable data such as medical images or parts of, signed consent forms or pseudonym lists are not to be sent via email (not even relayed to yourself), replicated and/or uploaded ir

Video, audio recordings and photography are not allowed for this research.

Clarifications

[redacted]

This clearance does[redacted]

All documents presented to your participants must include UOM's logo.

Since Dr Paul Bezzina, Dr Francis Zarb and Ms Deborah Mizzi may access personal data for verification purposes, they too must sign the Data Protection form.

This clearance does not allow verbal communications meaning that verbal consent is not covered.

This clearance is valid for your report to be included with your dissertation only and not in medical journals or elsewhere since you are not obtaining approval from MDH legal office.

Your submitted documentation must remain unchanged.

What was declared during this clearance process is what you will abide to.

You must abide with all the articles of the GDPR (EU) 2016 / 679 throughout the data collection process and thereafter.

You are requested to submit a copy of your findings to this office at the end of your study.

Please communicate with Ms Tiziana Muscat, Mr Claude Portanier Mifsud and Ms Marion Borg to present this clearance email.

To sign the data protection form, please contact Ms Graziella Aquilina through [redacted] *to provide the following:*

1. *This clearance email in PDF – to provide in PDF*
2. *CEO's approval in PDF - pending*
3. *The name of the Chairperson who approved your research - Dr Kenneth Saliba*
4. *The period of data collection – February 2022 – April 2022*
5. *Title of your research – The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol*
6. *The ID number for the following:- pending*
   - *Ms Leanne Galea*
   - *Dr Paul Bezzina*
   - *Dr Francis Zarb*
   - *Ms Deborah Mizzi*

NB: together with Dr Paul Bezzina, Dr Francis Zarb and Ms Deborah Mizzi, you must sign this form before starting

In summary – next step

1. Obtain approval from MDH CEO through [redacted]
2. Sign the Data Protection form at Ms Aquilina through [redacted] (please provide the above six points)

Regards

Simon Caruana
Senior Manager (Compliance)

L-Università ta' Malta

Seeking permission to perform Research Study

4 messages

Leanne Galea [redacted] 29 December 2021 at 17:37
To: [redacted]
Cc: Francis Zarb <[redacted]>, Paul Bezzina <[redacted]>, Deborah Mizzi <[redacted]>

Dear Ms. Falzon

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow-up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

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In line with ethical requirements, I would like to ask for your permission:

- So that I can identify and invite a radiographer to act as an intermediary person to access the picture archiving and c

MR cases and respective histo-pathological findings for the purpose of this study.

- For the intermediary person/s to contact the patient participants who are randomly selected, to obtain their informed consent to use their MR images, imaging reports and histo-pathological findings for the purpose of the study.
- For the intermediary person/s to retrieve their MR images and anonymise them to be used for the study.
- For the intermediary person/s to invite radiologists to participate in the image pathology identification and supply them with the anonymised images for image pathology identification.

Kindly note that permission and approval to conduct this study is also being sought from the Faculty of Health Sciences Research and Ethics Committee (FREC) and University Research Ethics Committee (UREC). I can assure you that all ethical issues would be considered and addressed throughout the study.

Should you wish any further information or clarification about the proposed study, please contact me on [redacted] or my supervisors; Dr. Francis Zarb [redacted] Dr. Paul Bezzina [redacted], Ms Deborah Mizzi [redacted]

Attached with this communication please find:

- Patient information letter and consent form both in English and Maltese
- Radiologist information letter and consent form in English
- Permission letter from the Chairperson of the Medical Imaging Department (MID)
- Permission letter from the Professional Lead, Radiography of the MID
- Permission letter from the Intermediary person/s
- One page proposal and Data collection tool
- Covering Letters in Maltese and English
- Permission letter from Data Protection Officer (MDH)

I thank you in advance,

Kind Regards,

Leanne Galea

9 attachments

- **Patient information sheet and consent form ENGLISH updated.pdf** 606K
- **Data collection tool updated.docx** 18K
- **Covering letter MALTESE.pdf** 352K
- **Covering letter ENGLISH .pdf** 349K

CAUTION: This email originated from OUTSIDE the Government Email Infrastructure. DO NOT CLICK LINKS or OPEN attachments unless you recognise the sender and know the content is safe.

[Quoted text hidden]

Leanne Galea [redacted] 3 January 2022 at 12:21
To: CEO at Health-MDH [redacted]

Dear Ms. Farrugia,

Email forwarded as requested.

Thank you,

Regards,

Leanne

[Quoted text hidden]

CEO at Health-MDH [redacted] 3 January 2022 at 13:09
To: Leanne Galea [redacted]

Dear Ms Galea,

Kindly note that approval has been given by Ms Celia Falzon for you to conduct this study in line with applicable hospital protocols.

Regards

Carmen Farrugia
Personal Assistant To CEO

ISPTAR MATER DEI

[redacted]
E carmen.farrugia@gov.mt

Mater Dei Hospital, Triq id-Donaturi tad-Demm, l-Imsida, Malta MSD 2090 | Tel +356 2545 0000 | https://deputyprimeminister.gov.mt/en/MDH/Pages/Home.aspx | https://www.facebook.com/materdeihospital/

Think before you print.

Appendix A2

Intermediary persons

Mr Claude Portanier Mifsud
Allied Health Professional
Medical Imaging Department

L-Università ta' Malta

22/11/2021

Dear Mr Portanier Mifsud

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

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In line with ethical requirements, I would like to ask if you would agree to act as the intermediary person for this proposed study. Your role as the intermediary person will be to:

- Identify the population and randomly select the sample of patient examinations retrospectively from the medical imaging picture archiving and communication system (PACS) and iSoft archive.
- Contact the patient participants who were randomly selected, to obtain their informed consent to use their MR images, imaging reports and histological findings for the purpose of the study.
- Provide the selected patient participants with an information letter and consent form.
- Retrieve their MR images, imaging reports and histological findings and anonymise them to be used for the study.
- Invite radiologists to participate and supply them with the anonymised images for image pathology identification.
- Collect the data following the image pathology identification.

Kindly note that permission and approval to conduct this study will be sought from the Faculty of Health Sciences Research and Ethics Committee (FREC) and University Research Ethics Committee (UREC DP). Permission from the Hospital chief executive officer (CEO) and Data Protection Officer (DPO) are also going to be obtained. I can assure you that all ethical issues would be considered throughout the study and addressed.

If you are in agreement to take on this role as an intermediary person, I kindly ask you to complete and sign this letter. Should you wish any further information or clarification about the proposed study, please contact me on +356 [redacted] by e-mail [redacted] or my supervisors; Dr. Francis Zarb [redacted] Dr. Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted]

I thank you in advance,

Kind Regards,

[redacted]

Leanne Galea
Researcher

DECLARATION BY INTERMEDIARY

I, CLAUDE PORTANIER MIFSUD declare that I accept responsibility to act as the intermediary for this study as described above and wish to do so from my own free-will.

22. NOV. 2021.
Date

[redacted]
Signature

L-Università ta' Malta

Seeking permission to act as Intermediary person

2 messages

Leanne Galea <leanne.galea.15@um.edu.mt> 23 November 2021 at 18:37
To: [redacted]

Dear Ms Borg

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes.

The target population will be patients who performed a breast MRI examination. Whilst the accessible population will include patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this is is when the most recent exams were performed using the updated full protocol on a 3-T Philips unit. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

A minimum of two radiologists specialised in breast imaging with a minimum of two years of experience in MRI breast reporting will be conveniently selected to evaluate the diagnostic accuracy of an abbreviated protocol when compared to the full protocol. The abbreviated protcol will be presented to the radiologists who will review the images and fill in the data collection tool for each set of images. The data collected from the abbreviated protocol will be compared with the data from the report issued from the MRI using the full protocol. Lesions with a final BI-RADS category of 1 or 2 will be considered as **negative** findings while those with a final BI-RADS of 3,4 or 5 will be considered **positive** findings. The findings will then be compared with the gold standard being the histo-pathological correlation of a breast lesion or at least 12 months of negative findings on follow-up imaging with either mammography, ultrasound or MRI in the absence of a biopsy.
In line with ethical requirements, I would like to ask if you would agree to act as the intermediary person for this proposed study. Your role as the intermediary person will be to:

- Identify the population and randomly select the sample of patient examinations retrospectively from the medical imaging picture archiving and communication system (PACS) and iSoft archive.
- Contact the patient participants who were randomly selected, to obtain their informed consent to use their MR images, imaging reports and histological findings for the purpose of the study.
- Provide the selected patient participants with an information letter and consent form.
- Retrieve their MR images, imaging reports and histological findings and anonymise them to be used for the study.
- Invite radiologists to participate and supply them with the anonymised images for image pathology identification.

- Collect the data following the image pathology identification.

Kindly note that permission and approval to conduct this study will be sought from the Faculty of Health Sciences Research and Ethics Committee (FREC) and University Research Ethics Committee (UREC DP). Permission from the Hospital chief executive officer (CEO) and Data Protection Officer (DPO) are also going to be obtained. I can assure you that all ethical issues would be considered throughout the study and addressed.

If you are in agreement to take on this role as an intermediary person, I kindly ask you to complete and sign this letter. Should you wish any further information or clarification about the proposed study, please contact me on [redacted] or my supervisors; Dr. Francis Zarb [redacted] Dr. Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted]

I thank you in advance,

Kind Regards,

Leanne Galea

Borg Marion at Health-MDH [redacted] 24 November 2021 at 10:16
To: Leanne Galea [redacted].mt>

Dear Leanne Galea,

I hereby accept the role of intermediary person to serve as an aid in your study.

Marion Borg

Allied Health Practitioner (Radiography)
Medical Imaging Department (Mammography)

[redacted]

From: Leanne Galea <[redacted]
Sent: 23 November 2021 18:37:02
To: Borg Marion at Health-MDH
Subject: Seeking permission to act as Intermediary person

CAUTION: This email originated from OUTSIDE the Government Email Infrastructure. DO NOT CLICK LINKS or OPEN attachments unless you recognise the sender and know the content is safe.

[Quoted text hidden]

L-Università ta' Malta

Leanne Galea [redacted]

Seeking permission to act as Intermediary person

2 messages

Leanne Galea [redacted] 24 November 2021 at 11:16
To: [redacted]

Dear Ms Muscat

I am a radiographer who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. As part of my final year of studies, I am required to conduct a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes.

The target population will be patients who performed a breast MRI examination. Whilst the accessible population will include patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. The specific period was chosen as this is is when the most recent exams were performed using the updated full protocol on a 3-T Philips unit. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

A minimum of two radiologists specialised in breast imaging with a minimum of two years of experience in MRI breast reporting will be conveniently selected to evaluate the diagnostic accuracy of an abbreviated protocol when compared to the full protocol. The abbreviated protcol will be presented to the radiologists who will review the images and fill in the data collection tool for each set of images. The data collected from the abbreviated protocol will be compared with the data from the report issued from the MRI using the full protocol. Lesions with a final BI-RADS category of 1 or 2 will be considered as **negative** findings while those with a final BI-RADS of 3,4 or 5 will be considered **positive** findings. The findings will then be compared with the gold standard being the histo-pathological correlation of a breast lesion or at least 12 months of negative findings on follow-up imaging with either mammography, ultrasound or MRI in the absence of a biopsy.
In line with ethical requirements, I would like to ask if you would agree to act as the intermediary person for this proposed study. Your role as the intermediary person will be to:

- Identify the population and randomly select the sample of patient examinations retrospectively from the medical imaging picture archiving and communication system (PACS) and iSoft archive.

- Contact the patient participants who were randomly selected, to obtain their informed consent to use their MR images, imaging reports and histological findings for the purpose of the study.
- Provide the selected patient participants with an information letter and consent form.
- Retrieve their MR images, imaging reports and histological findings and anonymise them to be used for the study.
- Invite radiologists to participate and supply them with the anonymised images for image pathology identification.
- Collect the data following the image pathology identification.

Kindly note that permission and approval to conduct this study will be sought from the Faculty of Health Sciences Research and Ethics Committee (FREC) and University Research Ethics Committee (UREC DP). Permission from the Hospital chief executive officer (CEO) and Data Protection Officer (DPO) are also going to be obtained. I can assure you that all ethical issues would be considered throughout the study and addressed.

If you are in agreement to take on this role as an intermediary person, I kindly ask you to complete and sign this letter. Should you wish any further information or clarification about the proposed study, please contact me on [redacted] or my supervisors; Dr. Francis Zarb [redacted] Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted]

I thank you in advance,

Kind Regards,

Leanne Galea

Muscat Tiziana at Health-MDH [redacted] 24 November 2021 at 11:21
To: Leanne Galea [redacted]

Dear Leanne,

I writing this email as an acceptance to act as an intermediary for this study.

Regards,
Tiziana Muscat
B.SC Hons Radiography

Fro [redacted]
Sen
To:
Subject: Seeking permission to act as Intermediary person

CAUTION: This email originated from OUTSIDE the Government Email Infrastructure. DO NOT CLICK LINKS or OPEN attachments unless you recognise the sender and know the content is safe.

[Quoted text hidden]

Appendix A3

FREC/UREC Approval

L-Università ta' Malta

Leanne Galea <[redacted]>

UREC-DP2201011FHS - FHS-2021-00038 Leanne Galea

Rita Pace Parascandalo [redacted] 2 March 2022 at 11:18
To: Leanne Galea <[redacted]>
Cc: Francis Zarb <[redacted]rch Ethics HEALTHSCI <research-[redacted]>

Dear Leanne,

your final revision was reviewed. Approval for your study is granted oBo FREC. You may proceed with your study and collect the data.

Good luck

Regards
Dr Rita PP

L-Università ta' Malta

Dr Rita Pace Parascandalo PhD (UCLan)
BSc(Hons) (Melit.), MSc(Melit.), RM

Senior Lecturer, Department of Midwifery
Chairperson, Faculty Research Ethics Committee

[redacted]

Appendix A4

Information and covering letters (English version)

L-Università ta' Malta

Patients` Information Sheet

Dear Participant,

My name is Leanne Galea, and I am currently reading for a M.Sc. Radiography area of specialisation- Breast Imaging at the University of Malta. As part of my course requirements, I am conducting a research study. My study is entitled **'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**.

Currently in Malta there is no programme available for breast screening (non-symptomatic patients) with MRI especially for high-risk patients. A full breast MRI protocol is performed for symptomatic patients who require further imaging after having a negative mammogram and/or ultrasound, follow up of breast cancer patients to assess for recurrence or to delineate the extent of a breast cancer. A full breast MRI protocol is a long scan (30 to 40 minutes) and is very expensive to perform therefore an abbreviated protocol will counteract these limitations by reducing the time and cost of each examination making it more applicable as a screening tool.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes.

The study is a mixed method, retrospective and comparative non-experimental study, evaluating and comparing the current full MRI breast imaging protocol to an abbreviated MRI breast protocol. The target population would be MR breast images of patients who performed a breast MRI examination. Whilst the accessible population will include MR breast images of patients who performed their breast MRI at the medical imaging department in a public general hospital in Malta between January 2019- December 2021. This period was chosen as this is when the most recent examinations were conducted using the full protocol. In this study the patient images, which will be used for the study, will be selected by using simple random sampling.

A minimum of two radiologists specialised in breast imaging with a minimum of two years of experience in MRI breast reporting will be conveniently selected to evaluate the diagnostic accuracy of an abbreviated protocol when compared to the full protocol. The abbreviated protocol will be presented to the radiologists who will review the images and fill in the data collection tool for each set of images. The data collected from the abbreviated protocol will be compared with the data from the report issued from the MRI using the full protocol. Lesions with a final BI-RADS category of 1 or 2 will be considered as negative findings while those with a final BI-RADS of 3,4 or 5 will be considered positive findings. The findings will then be compared with the gold standard being the histo-pathological correlation of a breast lesion or at least 12 months of negative findings on follow-up imaging with either mammography, ultrasound or MRI in the absence of a biopsy. Your participation in this study would help us gain a better understanding about the use of MRI as a screening tool.

You are being invited to participate in a study since you have recently performed an MRI of the breast between January 2019- December 2021. If you consent to participate, your MRI images, imaging reports and histological findings, will be pseudonymised meaning that the data will be assigned codes and that this data will be stored securely and separately from any codes and personal data which only the intermediary will have access to. The radiologists conducting the image quality evaluation will have access only to the anonymised images to evaluate the impact that the abbreviated protocol may have on diagnostic accuracy. You are not obliged to participate in this study, and you may withdraw from the study at any time without giving a reason. Furthermore, withdrawal from the study will not have any negative repercussions on you. I can assure you that confidentiality will be maintained throughout the study and that your identity and personal information will not be revealed in any publications, reports or presentations arising from this research.

A radiographer acting as the intermediary person will provide you with an information sheet. The intermediary person will also answer any questions which you may have. No harm or distress will be caused by your participation in this study. Participation in this study is completely voluntary and you are free to accept or refuse to take part without giving a reason. A copy of the information sheet and consent form will be provided for future reference. As a participant, you have the right, under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said regulation, to access, rectify and where applicable ask for the data concerning you to be erased. Once the study is completed and the results are published, the data will be retained in anonymous form. Any personal details will be destroyed in September 2022. Participation in this study would allow the researcher to assess if the diagnostic accuracy was maintained between the abbreviated and full protocol and scrutinize the suitability of the abbreviated protocol for future screening purposes.

This data may only be accessed by the researcher. The academic supervisor/s and the examiners will typically have access to coded data only. There may be exceptional circumstances which allow the supervisor and examiners to have access to personal data too, for verification purposes. If you want to enquire who accessed your data (including the two radiologists), please contact me on +[redacted] or my supervisors; Dr. Francis Zarb [redacted] Dr. Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted] Data files will be stored on the researcher's personal computer which is password protected and in an encrypted format. Any material in hard-copy form will be placed in a locked cupboard.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences at the University of Malta.

Thank you for your time and consideration.

Yours Sincerely

Leanne Galea

[redacted]

Leanne Galea	Dr. Francis Zarb	Dr. Paul Bezzina	Ms. Deborah Mizzi
Riċerkatriċi	Superviżur primarju	Superviżur tar-riċerka	Gwida

L-Università ta' Malta

Patients' Consent Form

'The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'

I, the undersigned, give my consent to take part in the study conducted by Leanne Galea. The purpose of this document is to specify the terms of my participation in this research study.

1. I have been given written and verbal information about the purpose of the study and all questions have been answered.
2. I understand that I have been invited to participate in a study, in which the researcher will perform tests to investigate the diagnostic accuracy obtained using the abbreviated protocol against the full protocol for breast MRI imaging as a screening alternative.
3. I am aware that the data collected will be coded and that this data will be stored securely and separately from any codes and personal data.
4. I am aware that the researcher is the only person who has access to this data. The academic supervisor/s and examiners will typically have access to coded data only. There may be exceptional circumstances which allow the supervisor and examiners to have access to personal data too, for verification purposes. If I want to enquire who accessed my data, I can contact the researcher on [redacted] or her supervisors; Dr. Francis Zarb [redacted], Dr. Paul Bezzina [redacted] and Ms Deborah Mizzi [redacted]
5. I am also aware that any data files will be stored on the researcher's personal computer that is password protected and in an encrypted format and no audio/video recordings will be used for data collection. Any material in hard-copy form will be placed in a locked cupboard and kept until results are published.
6. I am aware that my identity and personal information will not be revealed in any publications, reports or presentations arising from this research.
7. I also understand that I am free to accept, refuse or stop participation at any time without giving any reason. This will have no negative repercussions on myself and that any data collected from me will be erased. Data will be stored anonymously if it is impossible to delete (e.g. if it has already been anonymised).
8. I also understand that my contribution will serve to evaluate the suitability of an MRI abbreviated protocol for screening purposes.
9. A radiographer acting as an intermediary person will provide me with an information sheet and will answer any questions which might arise. No risks/discomfort are present in this study. I am aware that no additional harm or distress is expected by participating in this research study.
10. I understand that under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said regulation, I have the right to access, rectify, and where applicable ask for the data concerning me to be erased.
11. I also understand that once the study is completed and results are published the data will be retained in anonymous form. Any personal details will be destroyed in September 2022.
12. I will be provided with a copy of the information letter and consent form for future reference.
13. I have read and understood the points and statements of this form. I have had all the questions answered to my satisfaction, and I agree to participate in this study.

Participant: _____

Signature: _____

Date: _____

[redacted]

Leanne Galea	Dr. Francis Zarb	Dr. Paul Bezzina	Ms. Deborah Mizzi
Riċerkatriċi	Superviżur primarju	Superviżur tar-riċerka	Gwida

ISPTAR MATER DEI

Dear Participant,

I am a radiographer who is acting as an intermediary person for the researcher (Leanne Galea) who is currently reading for a M.Sc. Radiography area of specialisation - Breast Imaging at the University of Malta. The study is entitled '**The impact on diagnostic accuracy of an abbreviated screening breast Magnetic Resonance Imaging (MRI) protocol'**. I will be sending all the information on behalf of the researcher. The study is being carried out under the supervision of Dr. Francis Zarb, Dr. Paul Bezzina and Ms. Deborah Mizzi.

The aim of the study is to evaluate and compare the diagnostic accuracy obtained using an abbreviated protocol against the full protocol for breast MRI imaging for breast cancer screening purposes. You are being invited to participate in a study since you have recently performed an MRI of the breast between January 2019- December 2021. If you consent to participate, your MRI images, imaging reports and histological findings, will be accessed and anonymised to be used in the study to evaluate the impact that the abbreviated protocol may have on diagnostic accuracy. Attached with this letter you may find all the documents for your perusal.

You are not obliged to participate in this study, and you may withdraw from the study at any time without giving a reason. Furthermore, withdrawal from the study will not have any negative repercussions on you or on the care pathway within the hospital. I can assure you that confidentiality will be maintained throughout the study and that your identity and personal information will not be revealed in any publications, reports or presentations arising from this research.

If you consent to participate in this study please reply with the self addressed envelope attached. If you fail to respond by the end of January it will be taken as a negative reply. No participation in this study will not have any impact

Thank you for your time and consideration.
Yours Sincerely

Tiziana Muscat
Allied Health Professional (Radiographer)
Medical Imaging Department (MRI)

[redacted]

Appendix B

Data collection tool

Data collection tool- Image evaluation by radiologists

Image set number	Is there a lesion present? (Yes/ No)	If yes indicate location: Left (L) Right (R)/ Both (B) breasts	How many lesions are present on the specified breast/s?		In which quadrant is/are the lesion/s present ? (UOQ,UIQ, LOQ, LIQ, retroareolar region or axillary tail)		Size of lesion/s in mm (AP x TRA x CC)	Is there lymph node involvement? (Yes/No/Unsure)	Final BI-RADS score (0 to 6)
			Left Breast	Right Breast	Left Breast	Right Breast			
1									
2									
3									

Key: UOQ - upper outer quadrant
UIQ - upper inner quadrant
LOQ - lower outer quadrant
LIQ - lower inner quadrant

Key: AP - Antero Posterior
TRA - Transverse
CC - Cranio Caudal

Key: ABP- Abbreviated Protocol
FP- Full protocol

Data collection tool- Filled in from original report

Image set number	Is there a lesion present? (Yes/ No)	If yes indicate location: Left (L) Right (R)/ Both (B) breasts	How many lesions are present on the specified breast/s?		In which quadrant is/are the lesion/s present ? (UOQ,UIQ, LOQ, LIQ, retroareolar region or axillary tail)		Size of lesion/s in mm (AP x TRA x CC)	Is there lymph node involvement? (Yes/No/Unsure)	Final BI-RADS score (0 to 6)
			Left Breast	Right Breast	Left Breast	Right Breast			
1									
2									
3									

Key: UOQ - upper outer quadrant
UIQ - upper inner quadrant
LOQ - lower outer quadrant
LIQ - lower inner quadrant

Key: AP - Antero Posterior
TRA - Transverse
CC - Cranio Caudal

Key: ABP- Abbreviated Protocol
FP- Full protocol

Continuation of table- gold standard

Image set number	Histopathological findings			Follow up imaging	
	Left (L)/ Right (R)/ Both breasts (B)	Lymph Node involvement	BI-RADS Score	Imaging used	Negative (N) / Positive (P)
1					
2					
3					
4					

Appendix C

Reliability Results

Intra-rater reliability of each radiologist

Cohen's Kappa scores to evaluate intra-rater reliability for both radiologists

Variable	Radiologist	Kappa Value (n=10)	P value
Is there a lesion present?	1	0.600	0.048
	2	0.624	0.045
Is there lymph node involvement?	1	0.783	0.011
	2	1	0.002

*n=number of observations

ICC score to evaluate intra-rater reliability for both radiologists

Variable	Radiologist	ICC score (n=10)	P value
BI-RADS score	1	0.598	0.021
	2	0.969	0.0001

*n=number of observations

Inter-rater reliability of each radiologist

Cohen's Kappa scores to evaluate inter-rater reliability for both readings

Variable	Radiologist	Kappa Value (n=10)	P value
Is there a lesion present?	First reading	0.600	0.038
	Second reading	0.600	0.038
Is there lymph node involvement?	First reading	0.785	0.010
	Second reading	0.668	0.035

*n=number of observations

ICC score to evaluate intra-rater reliability for both readings

Variable	Radiologist	ICC score (n=10)	P value
BI-RADS score	First reading	0.444	0.086
	Second reading	0.832	0.0001

*n=number of observations

Appendix D1

Location (right/ left) and number of lesions results for both protocols

	Full vs Abbreviated protocol	Left/ Right or Both breast	Number of lesions on each breast
Case 1	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 2	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	Right	1
	Abbreviated B		1
Case 3	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Both	2- left, 1- right
	Abbreviated B	Both	3-left, 1-right
Case 4	Gold standard	Left	2
	Full	Left	3
	Abbreviated A	Left	3
	Abbreviated B	Left	3
Case 5	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	2
	Abbreviated B	Left	1
Case 6	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 7	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	Right	1

Case 8	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 9	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 10	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	Right	2
Case 11	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 12	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	2
Case 13	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1
	Abbreviated B	Right	1
Case 14	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	Left	1
Case 15	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/

	Abbreviated B	Right	1
Case 16	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	2
	Abbreviated B	Left	2
Case 17	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1
	Abbreviated B	Right	2
Case 18	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 19	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 20	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 21	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 22	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 23	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1

	Abbreviated B	Right	1
Case 24	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1
	Abbreviated B	Right	1
Case 25	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	Left	2
	Abbreviated B	Left	2
Case 26	Gold standard	Right	1
	Full	Right	2
	Abbreviated A	Right	2
	Abbreviated B	Right	2
Case 27	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 28	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	Right	1
	Abbreviated B	/	/
Case 29	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 30	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 31	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	Left	1

	Abbreviated B	Left	1
Case 32	Gold standard	No lesion	0
	Full	/	/
	Abbreviated A	/	/
	Abbreviated B	/	/
Case 33	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1
	Abbreviated B	Right	1
Case 34	Gold standard	Left	1
	Full	Left	1
	Abbreviated A	Left	1
	Abbreviated B	Left	1
Case 35	Gold standard	Right	1
	Full	Right	1
	Abbreviated A	Right	1
	Abbreviated B	Right	1

Appendix D2

Size and breast localisation results for both protocols

	Full vs Abbreviated protocol	Localisation	Size
Case 1	Full	Left UOQ	3cm
	Abbreviated A	Left UOQ	1.2cm AP x4.4cm transverse x3.9cm CC
	Abbreviated B	Left UOQ/ Retroareolar/ L 3o'clock position	1.1cm AP x4.6cm transverse x3.9cm CC
Case 3	Full	Left UOQ	1.5cm
	Abbreviated A	Right deep retroareolar Left 1st lesion-Left supra-areolar Left 2nd lesion- LOQ	**Right**- 1.5 cm AP x0.6cm transverse x 1.0cm CC **Left 1st lesion**-0.9 cm AP x1.7 cm transverse x 1.3cm CC **Left 2nd lesion**- 0.8 cmAP x 0.5cm transverse x 0.7 cm CC
	Abbreviated B	Right UOQ Left 1st lesion-Left supra-areolar Left 2nd lesion- 9o'clock Left 3rd lesion- Left UOQ/ 3o'clock	**Right**- 1.2 cm x0.5cm **Left 1st lesion**-0.5 cm x1.5 cm **Left 2nd lesion**- 1.4 cm x0.3 cm **Left 3rd lesion**- 0.6 cm focus
Case 4	Full	1st lesion-Left UOQ 2nd lesion-retroareolar region 3rd lesion-Left LOQ	**1st lesion**-1.8 cm AP, 1.8 cm transverse, 1.7 cm CC **2nd lesion**-0.8 cm AP, 0.8 cm transverse, 0.8 cm CC **3rd lesion**- 0.5 cm AP,

			0.5 cm transverse, 0.5 cm CC
	Abbreviated A	1st lesion-Left axillary tail / Left UOQ 2nd lesion-retroareolar region (cranial) 3rd lesion-retroareolar region (caudal)	**1st lesion**-1.5 cm AP x1.1 cm transverse x 1.7cm CC **2nd lesion**-0.6 cm AP x1.0 cm transverse x 1.5cm CC **3rd lesion**- 0.6 cm AP x 0.6cm transverse x 0.4cm CC
	Abbreviated B	1st lesion-Left UOQ 2nd lesion-retroareolar region 3rd lesion-Left infraareolar region	**1st lesion**-1.7 cm x1.8 cm **2nd lesion**-0.9 cm x0.8 cm **3rd lesion**- 0.4 cm
Case 5	Full	Left UOQ	N/A
	Abbreviated A	Both lesions retroareolar region	**1st lesion** (cranial)-0.9cm AP x 1.0cm transverse x 0.9 cm CC **2nd lesion** (caudal)-0.4cm AP x 0.6cm transverse x 0.5cm CC
	Abbreviated B	Left UOQ/ Retroareolar region	1.0 cm transverse x 0.8 cm AP
Case 8	Full	Retroareolar region	1.8 cm AP, 3.0 cm transverse, 2.0 cm CC
	Abbreviated A	Left LIQ	2.5 cm AP, 3.0 cm transverse, 2.5 cm CC
	Abbreviated B	Supra-areolar region	2.0 cm AP, 3.1 cm transverse, 2.7 cm CC
Case 9	Full	Left LOQ	4.4cm AP x 3.1cm CC

	Abbreviated A	Left LOQ	4.1cm AP x 3.4cm transverse x 3.2cm CC
	Abbreviated B	Left LOQ	2.7cm transverse, 4.0cm AP x 3.1cm CC
Case 11	Full	Left UOQ	8cm AP, 2.1cm transverse, 4 cm CC
	Abbreviated A	Retroareolar to Lt UOQ	6.7cm AP, 3.2cm transverse, 4.5 cm CC
	Abbreviated B	Left UOQ/ 3 o'clock position	7.5cm AP, 2.7cm transverse, 4 cm CC
Case 12	Full	Retroareolar region	1.3cm x 0.9 cm
	Abbreviated A	Supraareolar region	1.4cm APx1.3cm transverse x 1.6cm CC
	Abbreviated B	1st lesion-Left UIQ 2nd lesion-3o'clock	**1st lesion**-1.2cm APx1.2cm transverse x 1.3cm CC **2nd lesion**-5x4mm
Case 13	Full	Right UOQ	0.9cm x0.7cm
	Abbreviated A	Right UOQ	0.9cm AP x0.9cm trans x 0.8cm CC
	Abbreviated B	Right UOQ	1.4cm AP x1.3cm trans x1.4cm CC
Case 16	Full	Left UOQ	1.2cm x 1.4cm
	Abbreviated A	Both Left UOQ	**1st lesion** (posterior)-1.0cm APx1.6cm transverse x 1.1cm CC **2nd lesion** (anterior) - 0.4cm AP x0.5cm transverse x 0.5cm CC
	Abbreviated B	Both Left UOQ	**1st lesion**-1.0cm APx1.4cm transverse x 1.5cm CC

			2nd lesion-0.4cm x0.6cm
Case 17	Full	Right LOQ (8/9 o clock)	2.6cm AP, 1.4cm transverse, 1.5 cm CC
	Abbreviated A	Lateral retroareolar	2.8cm AP x1.1cm transverse x 1.7cm CC
	Abbreviated B	1st lesion- Right LOQ 2nd lesion- Right UOQ	**1st lesion**-3.3cm AP x1.8cm transverse x 1.4cm CC **2nd lesion**- 1 cm AP x1 cm transverse x 1 cm CC
Case 20	Full	Right UOQ (2/3 o'clock)	4.2cm AP, 1.5 cm transverse, 2.3cm CC
	Abbreviated A	Right UOQ	2.9cm AP, 1.9 cm transverse, 2.4cm CC
	Abbreviated B	Right UOQ extending to surpaareolar region	4.5cm AP, 2.1 cm transverse, 3.4cm CC
Case 21	Full	Supraareolar region	1.3cm x 0.8cm
	Abbreviated A	Supraareolar region	0.9cm AP, 0.9 cm transverse, 1.0cm CC
	Abbreviated B	12o'clock / supraareolar region	0.9cm AP, 0.5 cm transverse, 0.8cm CC
Case 23	Full	Right UIQ	3.5cm x 1.8cm
	Abbreviated A	Right UIQ	3.6cm AP, 1.9 cm transverse, 2.2cm CC
	Abbreviated B	Right UIQ	5.6cm AP, 2.0 cm transverse, 2.6cm CC
Case 24	Full	Right UOQ	4.4cm APx 3.1 cm transverse x 2.8 cm CC
	Abbreviated A	Right UOQ	1.3m AP, 0.8 cm transverse, 1.1 cm CC

	Abbreviated B	Right UOQ	2.0m AP, 1.3 cm transverse, 1.2cm CC
Case 26	Full	1st lesion - Right UIQ 2nd lesion- Right UOQ	**1st lesion** -1.2cm x 0.8cm **2nd lesion**- 1.2cm x 1.0cm
	Abbreviated A	1st lesion -Right UIQ 2nd lesion- 9o'clock	**1st lesion** -1.0 cm AP x 1.2 cm transverse x 1.2cm CC **2nd lesion**- 1.0cm AP x 1.4cm transverse x 0.8mm CC
	Abbreviated B	1st lesion -Right UIQ 2nd lesion- 9o'clock/ Right UOQ	**1st lesion -**1.4 cm AP x 0.9cm transverse x 1.6cm CC **2nd lesion**- 1.4cm AP x 1.0cm transverse x 0.8mm CC
Case 29	Full	Retroareolar region	1.4cm x 1.0cm
	Abbreviated A	Retroareolar region	1.1 cm AP x 1.1cm transverse x 1.0cm CC
	Abbreviated B	Retroareolar region	1.2 cm AP x 1cm transverse x 1.5cm CC
Case 33	Full	Supraareolar and retroareolar r region	4.8 AP x 7.4 transverse x 5.5 CC
	Abbreviated A	Retroareolar region	4.2 AP x 4.4 transverse x 4.6 CC
	Abbreviated B	Retroareolar region	3.2 AP x 6.4 transverse x 4.2 CC
Case 34	Full	Axillary tail	1.2cm AP x0.8cm transverse x 1.1cm CC
	Abbreviated A	Axillary tail	0.9 cm AP x 0.7 cm transverse x 0.9cm CC

	Abbreviated B	Left UOQ	1.0 cm AP x 1.0 cm transverse x 1.3cm CC
Case 35	Full	Right UOQ	0.6cm x 0.4cm
	Abbreviated A	Right UOQ	1.1 cm AP x 0.5 cm transverse x 0.7cm CC
	Abbreviated B	Right UOQ	1.1 cm AP x 0.5 cm transverse x 0.8cm CC