Breast lesion elastography region of interest selection and quantitative heterogeneity: A systematic review and meta-analysis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Dedication

To the soul of my Father, may Allah bless him

To my father who could not see this thesis completed. We'll always remember that special smile,

that caring heart,

that warm embrace

You always gave us

We will never forget your favour

List of Contents

Subject *Page No.*

List of Abbreviations ..... **i**

List of Tables ..... **iii**

List of Figures ..... **iv**

Introduction **1**

Aim of the Work **3**

Review of Literature

Embryology and Anatomy of the Breast 4

Pathology of Breast 22

Elastography 31

Methods **50**

Results **69**

Discussion **81**

Summary **91**

Conclusion **93**

Recommendations **94**

References **95**

Arabic Summary ..... **—**

List of Abbreviations

Abbr.	Full-term
ARFI	**:** Acoustic radiation force impulse
BI-RADS	**:** Breast Imaging-Reporting and Data System
DOR	**:** Diagnostic odds ratio
DTA	**:** Diagnostic test accuracy
ELDU	**:** Extra lobular terminal duct
ES	**:** Elastographic scoring
FNR	**:** False-negative rate
FOV	**:** Field of view
FP	**:** False positives
FPR	**:** False-positive rate
HER2	**:** Human epidermal growth factor receptor 2
ILDU	**:** Interlobular ductal unit
MRI	**:** Magnetic resonance imaging
NAC	**:** Neoadjuvant chemotherapy
NAC	**:** Nipple-areola complex
PRISMA	**:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROC	**:** Receiver operating characteristic curve
ROI	**:** Region of interest
SWE	**:** Shear wave elastography
TDLU	**:** Terminal ductal lobular unit
TN	**:** True negatives

TP **:** True positives

US **:** Ultrasound

USG **:** Ultrasonography

VTIQ **:** Virtual touch imaging quantification

VTTQ **:** Virtual touch tissue quantification

1D-SWE **:** One-dimensional transient elastography

2D **:** Two-dimensional

2D-SWE **:** Two-dimensional shear wave elastography

List of Tables

Table No.	Title	Page No.
Table (1):	Characteristics of include studies	56
Table (2):	Reported Sensitivity, Specificity, FPR and FNR of breast elastography for different outcome parameters	62
Table (3):		80

List of Figures

Figure No.	Title	Page No.
Figure (1):	Ectodermal streaks develop from axilla to groin	4
Figure (2):	Development of epithelial buds and bud branching	5
Figure (3):	The position of the mammary line (Milk line from the axilla to the groin)	6
Figure (4):	Overview of breast anatomy	8
Figure (5):	Internal anatomy of the breast: mammographic illustrations	8
Figure (6):	The suspensory ligaments	9
Figure (7):	Sagittal graphic shows components of a lobe/segment from duct orifice on the nipple surface to the TDLUs	12
Figure (8):	Schematic diagram of the distal ductal branches and TDLU	13
Figure (9):	The arterial supply and venous drainage of the breast	16
Figure (10):	Normal lymphatic anatomy of the breast.	20
Figure (11):	Normal sonographic components of the breast gland.	21
Figure (12):	Lipoma.	25
Figure (13):	Fibroadenoma	26

Figure (14): Shear wave elastographic evaluation of a BI-RADS III biopsy-proven fibroadenoma 27

Figure (15): Images of fibroadenoma in a 43-year-old woman 27

Figure (16): Shear wave elastographic examination of two BI-RADS IV lesions that proved to be grade 1 invasive ductal carcinoma 29

Figure (17): Images of invasive ductal carcinoma in a 44-year-old woman..... 30

Figure (18): The effect of optimal and suboptimal displacement/release compression in strain elastography 33

Figure (19): The effect of pre-compression on stiffness values 34

Figure (20): Change of breast lesion size on elastography 36

Figure (21): Difficulty in evaluating benign lesions in fibroglandular tissue..... 39

Figure (22): Strain ratio (SR) as a semi quantitative method in strain elastography 41

Figure (23): Stiffness patterns seen in elastography of breast cancers..... 42

Figure (24): Value of a quality measure in shear wave elastography (SWE) of breast lesions 42

Figure (25): Shear wave elastographic evaluation of a BI-RADS IV biopsy-proven sclerosing intraductal papilloma 45

Figure (26): Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of screening and study selection process 53

Figure (27): Forest plot of 2 Emax. 72

Figure (28): Summary ROC Plot of Emax. 73

Figure (29): Forest plot of Emean. 74

Figure (30): Summary ROC Plot of Emean. 75

Figure (31): Forest plot of Eratio. 76

Figure (32): Summary ROC Plot of Eratio. 77

Figure (33): Forest plot of for comparison of Emean and Emax (paired data only). 78

Figure (34): Summary ROC Plot for comparison of Emean and Emax tests (paired data only). 79

Figure (35): Post- test probability of breast cancer as a function of reported prevalence of the condition per study 80

Abstract

Background: Breast cancer is one of the most common causes of death among women worldwide. Early detection and diagnosis will be helpful to reduce mortality and improve prognosis. It is urgent to develop efficient detection technology for breast cancer. Mammographic screening is a valuable tool for early detection of breast cancer. However, the increased density of breast tissue significantly reduces the diagnostic accuracy.

Objective: to provide an overview of the different reported elasticities of specific breast pathologies based on ultrasound elastography

Methods: A total of 35 articles including 8316 patients and 9057 breast lesions were included in the pooled analysis of which 3060 malignant lesions were included from 40 studies. The median incidence of malignant breast lesion is 37.1% calculated from the incidence of malignant lesions of all included studies. Seven of the included studies assessed VTIQ. Mean age varied along all included studies.

Results: The sensitivity and specificity of Emax, Emean and Eratio for the diagnosis of breast cancer varied according to the interpretative criteria used to define a test as positive. The summary estimates of sensitivity and specificity were 82.58% (95% CI 78.32%% to 86.16%) and 84.12% (95% CI 79.07% to 87.07%) for Emean, 86.19% (95% CI 81.60%to 89.77%) and 88.56% (95% CI 88.56% to 91.54%) for Emax, and 87.50% (95% CI 77.47%to 93.44%) and 79.30% (95% CI 68.21% to 87.24%) for Eratio respectively. Regarding DOR, Emax achieved the highest value 48.32 (95% CI 28.7 to 67.8) which means There are 48 times the odds of obtaining an Emax positive result in a diseased rather than a non-diseased person. Meta-regression analysis was conducted to assess the impact of two covaries; Emean and Emax using Likelihood ratio test and revealed significant difference existed with higher summary sensitivity (X^2= 35.04, p<001) and specificity (X^2= 18.65, p<001) in Emax than Emean. SROC curves were used to show the distribution of sensitivity and specificity of Emax, **Conclusion:** Our meta-analysis demonstrates that SWE is an accurate and reliable diagnostic tool in discriminating malignant and benign breast lesions. With wide application, SWE may significantly improve the early diagnostic of breast cancer. SWE can provide additional information on predicting breast cancer prognosis.

Key words: Breast, lesion, elastography, quantitative heterogeneity

Introduction

With costs and incidences of breast diseases ever increasing, improved methods of differential diagnosis based on quantitative measures of elasticity have been gaining support and interest for clinical utilization. Numerous studies have reported lower stiffness of benign masses compared to their relatively stiff and malignant counterparts, establishing a widely-accepted correlation between the measured elasticity of a mass and its pathology **(O'Hagan and Samani, 2009).** Shear wave elastography (SWE) is the most widely utilized clinical method of measuring in vivo tissue elasticity. The traditional metrics of lesion elasticity from SWE include the mean, maximum and/or the relative elasticity of the lesion to the adjacent parenchyma (strain ratio) **(Barr et al., 2015).**

Each of these three measures has been evaluated for utility in improving the specificity of breast lesion diagnosis. Strain ratio has also demonstrated clinical utility in differential diagnosis **(Sadigh et al., 2012),** but combines the elasticities of the pathologic with healthy adjacent tissues. There is evidence to suggest that the pathology of the lesion also affects the mechanics of the surrounding tissues **(Zhou et al., 2014)** and therefore the ratios of stiffness may not be optimal for stratification of malignancy risk. Mean and maximum measures of elastic modulus are generally useful in confirming cases with very high (malignant) or very low (benign) stiffness, but neither measure can consistently discern malignancy alone. Of these studied metrics, maximum elasticity has demonstrated the

greatest promise in differential diagnosis and will be considered the metric against which new metrics should be evaluated **(Berg et al., 2012).**

Different studies have identified a wide range of thresholds for discriminating benign from malignant conditions – ranging from 50 kPa **(Evans et al., 2013)** to 82.3 kPa **(Lee et al., 2013)** based on the mean malignancy stiffness.

Meta-analysis is the statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, meta-analysis can be used to identify this common effect. When the effect varies from one study to the next, meta-analysis may be used to identify the reason for the variation ***(Haidich, 2010).***

Although a growing corpus of literature encourages the inclusion of elasticity in clinical practice based on observed improvements in diagnostic specificity **(Barr et al., 2012; Berg et al., 2012; Burnside et al., 2007; Sadigh et al., 2012),** improved metrics and standardization are needed to facilitate the use of these technologies and to address the significant variability that confounds early clinical results **(Vreugdenburg et al., 2013).** Lesion heterogeneity has been acknowledged as a potentially useful measure and has been assessed both qualitatively and semi-quantitatively **(Berg et al., 2012; Lee et al., 2013).**

Aim of the Work

The purpose of this systematic review and metaanalysis was therefore to (i) provide an overview of the different reported elasticities of specific breast pathologies based on ultrasound elastography, (ii) evaluate the relationship of ROI selection to the reported elasticity metrics and (iii) evaluate a new metric of elasticity heterogeneity to improve the discrimination between benign and malignant conditions.