

Retrospective analysis of suspicious non palpable breast lesions from: the initial years of the Breast Unit in Malta

Angela Sultana, Gordon Caruana Dingli, Victor Grech

Abstract

Aim: The aim of this retrospective study was to analyse the false positive rate of suspicious non palpable breast lesions detected by ultrasonography and mammography.

Method: The data was collected from the first seven years (2000-2007) since the set up of the Breast Unit in Malta.

Results: The results showed that the false positive rate for suspicious breast lesions detected by ultrasound and mammography were 84% and 57.6% respectively. The overall false positive rate was 62.5%.

Conclusion: The overall false positive rate for suspicious breast lesions detected by both radiographic modalities is high in our unit when compared to that of other centres. Suggestions for improvement are discussed.

Keywords

Biopsy, breast, neoplasm, mammography, sensitivity and specificity, ultrasonography

Angela Sultana MD, FRCS (Edin)
Surgical Department, Mater Dei Hospital, Malta
Email: angiesultana@yahoo.com

Gordon Caruana Dingli MD, FRCS, RCP&S (Glasg)
Surgical Department, Mater Dei Hospital, Malta

Victor Grech PhD, FRCPC
Paediatric Department, Mater Dei Hospital, Malta

* corresponding author

Introduction

Screening mammography has become commonplace in the routine health management of women world-wide. More than 600,000 women undergo breast biopsies globally annually. 20-40% of these are for non-palpable breast lesions.¹ The early detection and management of non palpable breast lesions suspected to be malignant has therefore become an important issue. Guide wire localization (GWL) followed by excision was introduced in 1985, and has remained the preferred technique for treatment of non palpable mammographically (mammo) and ultrasonographically (US) detected breast lesions.¹ This method has remained the gold standard against which more modern biopsy techniques of suspicious non palpable breast lesions are compared.

In Malta, the Breast Clinic was set up in January 2000, initially at St. Luke's Hospital, now at Mater Dei Hospital. On average, 25 new cases are seen per week, including symptomatic and screen detected problems. This results in approximately 1300 new cases annually.

Aim

This retrospective single centre study analysed false positive rates of suspicious non palpable breast lesions detected on ultra sound and mammography for the period January 2000 to December 2007. Female patients who were found to have suspicious breast lesions on routine or screening mammography or ultrasonography requiring localisation biopsy were studied. The local experience, trends and outcomes were analysed.

Methods

Patient records for those patients attending the Breast Clinic for the period January 2000 to December 2007 were retrospectively reviewed after obtaining a list of patients who underwent guide wire localization (GWL) of impalpable breast lesions at the Imaging Department. The patients seen at the Breast Clinic and included in this study were all operated by the Breast Care Team. Data regarding patient characteristics, clinical assessment, type of localisation performed, histology of biopsy specimen and further management performed was collected and entered into an Excel spreadsheet.

GWLs were all performed by 3 experienced radiologists with an interest in breast disease. Using Kopan's Hook, US localisation was done by means of a hand held US probe while

mammographic localisation was performed using the grid technique. Two cohorts were identified: those with suspicious palpable lesions detected by mammography (mammo GWL group) and a second cohort with suspicious non palpable lesions detected by US (US GWL group).

Definitions

A redo GWL implies that the radiograph of the biopsy specimen did not include the suspect lesion or microcalcifications seen in the original radiograph, or else that repeat mammogram during follow up showed the same lesions thereby necessitating a repeat localisation.

A lesion on ultrasound was regarded as suspicious if it was hypoechoic with irregular outlines and/or dorsal acoustic shadowing.

A lesion on mammography was regarded as suspicious if it showed a cluster of fine microcalcifications or a spiculated lesion.

An adequate biopsy specimen implies the presence of in situ or invasive malignancy .

A true positive implies that the suspicious lesion on US or mammogram was confirmed to be malignant on histology. A false positive implies that the lesion visualised on US or mammography was regarded as suspicious and proven to be benign on histology.

Statistical analysis

Medians as well as means were used as some data variables were moderately skewed. T-tests were used to compare means. Fischer's and χ^2 tests were used to compare proportions. A *p* value ≤ 0.05 was considered statistically significant.

Results

A national breast screening programme had not been set up when this study was conducted. Breast screening is offered to "high risk" women referred by general practitioners to the Breast Clinic. A considerable number of women undergo opportunistic breast screening at private clinics and are referred to the Breast Clinic for surgery. All suspicious mammograms are reviewed at the multi-disciplinary breast meeting and the decision to perform GWL is taken there. A substantial number of women who have had private mammograms are told that they require biopsy and this decision is respected by the team.

One hundred and twenty-six patients underwent GWL of suspicious non palpable breast lesions at the Breast Unit between January 2000 and December 2007.

One hundred and one cases underwent a mammographically guided localisation procedure. The remaining 25 patients had US detected suspicious lesions and localisation was therefore performed under US guidance. Overall, 136 GWLs were performed (Table 1). Figure 1 demonstrates the trend regarding type and number of GWLs performed during the 7 year study period. This graph shows that during the study period there was a progressive increase in the number of mammographic GWLs performed but a slow increase in the number of ultrasonographic GWLs . The

Table 1: Guide wire localization: patients and numbers

	US GWL	Mammo GWL	Total
Patients (n)	25 (19.8%)	101 (80.2%)	126
GWLs (n)	25 (18.3%)	111 (81.6%)	136

GWL: Guide wire localizations, *US:* ultrasound, *Mammo:* mammography

maximum number of GWLs was performed in 2006 followed by a sharp drop in 2007.

Table 2 summarises the patient characteristics of both cohorts.

In the mammo GWL group, 10 extra procedures were performed. Four patients required simultaneous bilateral localisations, and another 5 patients needed a redo GWL, one of which had 2 redos. The mammo GWL had a redo rate of 5.4% compared to the US group which had a redo rate of 0% (*p*=ns). The absence of redoes in the US group is due to the fact that the specimen is not subjected to US analyses. Four patients (3.9%) in the mammo GWL cohort required simultaneous bilateral localisations. Therefore the redo mammo GWL accounted for 5.4% of this group and 4.4% of the total GWL procedures. Table 3 demonstrates the clinical features of the 2 groups of patients.

Mammo GWL group

Twenty-three (22.7%) out of 101 patients who had a routine/ screening mammography had an US of the breast performed at the same time or soon after. Sixteen of these had a lesion detectable on US too. After a mammographically controlled GWL, 4 of this group had malignant pathology and one was atypical ductal hyperplasia (ADH). Out of the 7 which did not reveal a lesion on US only one had an abnormal pathology of atypical ductal hyperplasia after mammographic GWL.

Figure 2 shows the relative distribution of the mammogram GWL breast lesions. Fifty-one (45.9%) lesions were located in the upper outer quadrants. In this cohort, histologically, 43 of these suspicious non palpable lesions were malignant and 4 were reported as atypical ductal hyperplasia. For statistical purposes therefore, this cohort had 47 abnormal lesions (42.3%). Twenty-three (48.9%) with abnormal pathology were located in the upper outer quadrants but this was not statistically significant. This cohort of patients had a true positive rate of 42.3% and a false positive rate of 55.6%.

US GWL group

Twenty patients (80%) of this cohort of 25 patients also had a mammogram performed. A non palpable breast lesion was also evident on the mammogram in 8 of this group of patients. Thus 32% of the US GWL group had lesions evident on both radiological modalities. Four (16%) of all these suspicious non palpable breast lesions were malignant on histology. Therefore

ROTATEQ® Rotavirus vaccine (live, oral)
ABRIDGED PRODUCT INFORMATION
Please refer to Summary of Product Characteristics (SPC) before prescribing

PRESENTATION

Oral Solution

2 ml solution in a pre-filled squeezable tube (LDPE), with a twist-off cap (HDPE) in a protective bag, pack size of 1

One 2-ml dose contains:

rotavirus serotype* G1 not less than 2.2 x 10⁶ IU1, 2
rotavirus serotype* G2 not less than 2.8 x 10⁶ IU1, 2
rotavirus serotype* G3 not less than 2.2 x 10⁶ IU1, 2
rotavirus serotype* G4 not less than 2.0 x 10⁶ IU1, 2
rotavirus serotype* P1[8] not less than 2.3 x 10⁶ IU1, 2
* human-bovine rotavirus reassortants (live), produced in Vero cells.

¹ Infectious Units

² As lower confidence limit (p = 0.95)

Excipient:

This product contains sucrose 1080 mg

USES: RotaTeq is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infection. In clinical trials, efficacy was demonstrated against gastroenteritis due to rotavirus of serotypes G1P1[8], G2P[4], G3P1[8], G4P1[8], and G9P1[8]. The use of RotaTeq should be in accordance with official recommendations.

DOSAGE AND ADMINISTRATION. Posology:

Three doses of RotaTeq should be administered. The first dose may be administered from the age of six weeks and no later than the age of 12 weeks. RotaTeq may be given to infants who were born prematurely provided that the period of gestation was at least 25 weeks. These infants should receive the first dose of RotaTeq at least six weeks after birth. There should be intervals of at least 4 weeks between doses. It is preferable that all three doses should be administered before the age of 20-22 weeks. All three doses should be given by the age of 26 weeks. As no data exist regarding the interchangeability of RotaTeq with another rotavirus vaccine, it is recommended that infants who receive RotaTeq for the first immunisation against rotavirus should receive this same vaccine for the subsequent doses. If it is observed or strongly suspected that an incomplete dose has been swallowed (e.g., infant spits or regurgitates the vaccine), a single replacement dose may be given at the same vaccination visit, however, this has not been studied in clinical trials. If the problem recurs, additional replacement doses should not be given.

No further doses are recommended after completion of the 3-dose series. Method of administration: For oral administration only. RotaTeq SHOULD UNDER NO CIRCUMSTANCES BE INJECTED. RotaTeq may be given without regard to food, liquid, or breast milk.

CONTRA-INDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity after previous administration of rotavirus vaccines.
- Previous history of intussusception.
- Subjects with congenital malformation of the gastrointestinal tract that could predispose to intussusception.
- Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of RotaTeq. However, in the absence of sufficient data, administration of RotaTeq to asymptomatic HIV subjects is not recommended.
- Administration of RotaTeq should be postponed in infants suffering from acute severe febrile illness. -The presence of a minor infection is not a contraindication for immunisation. The admin-

istration of RotaTeq should be postponed in subjects suffering from acute diarrhoea or vomiting.

PRECAUTIONS

No safety or efficacy data are available regarding administration of RotaTeq to immunocompromised infants, infants infected with HIV or infants who have received a blood transfusion or immunoglobulins within 42 days of dosing. In trials, RotaTeq was shed in the stools of 8.9 % of vaccine recipients almost exclusively in the week after dose 1 and in only one vaccine recipient (0.3 %) after dose 3. Peak excretion occurred within 7 days of dosing. It is theoretically possible that transmission of vaccine virus may occur to seronegative contacts. RotaTeq should be administered with caution to individuals with close contacts who are immunodeficient (e.g., individuals with malignancies or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy). Also, those caring for recent vaccinees should observe careful hygiene especially when handling excreta. In a clinical study, RotaTeq was administered to approximately 1,000 infants who were born at a gestational age of 25 to 36 weeks. The first dose was administered from 6 weeks after birth. The safety and efficacy of RotaTeq were comparable between this subset of infants and infants born at term. Safety or efficacy data are not available for infants with active gastrointestinal illnesses (including chronic diarrhoea) or growth retardation. Administration of RotaTeq may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk. The level of protection provided by RotaTeq is based on the completion of all 3 doses. As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients. RotaTeq does not protect against gastroenteritis due to other pathogens than rotavirus. No clinical data are available on the use of RotaTeq for post-exposure prophylaxis. RotaTeq contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this vaccine. The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed. Co-administration of RotaTeq with vaccines containing one or more of the following antigens at approximately 2, 4 and 6 months of age demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected: Diphtheria-tetanus-acellular pertussis vaccine (DTaP), Haemophilus influenzae type b vaccine (Hib), Inactivated poliomyelitis vaccine (IPV), Hepatitis B vaccine (HBV) and Pneumococcal conjugate vaccine (PCV). Co administration of RotaTeq with DTaP-IPV-HBV-Hib vaccine (Infanrix hexa) at approximately 2, 3, and 4 months of age demonstrated that the immune responses and the safety profiles of the co administered vaccines were unaffected compared to separate administrations. Co administration of RotaTeq with a group C meningococcal conjugate vaccine (MenCC, the vaccine studied was a tetanus toxoid conjugate) at 3 and 5 months of age (and mostly at the same time as DTaP-IPV-Hib vaccine), followed by a third dose of RotaTeq at approximately 6 months of age, demonstrated that the immune responses to RotaTeq and MenCC were unaffected. Co administration resulted in an accept-

able safety profile. Concomitant administration of RotaTeq and oral poliomyelitis vaccine (OPV) did not affect the immune response to the poliovirus antigens. Although concomitant administration of OPV slightly reduced the immune response to rotavirus vaccine, there is currently no evidence that clinical protection against severe rotavirus gastroenteritis would be affected. The immune response to RotaTeq was unaffected when OPV was administered two weeks after RotaTeq. Therefore, RotaTeq can be given concomitantly with monovalent or combination infant vaccines containing one or more of the following antigens: DTaP, Hib, IPV or OPV, HBV, PCV and MenCC.

Pregnancy and lactation: RotaTeq is intended for use in infants only. Thus human data on use during pregnancy or lactation are not available and animal reproduction studies have not been performed. SIDE

EFFECTS. Refer to SPC for complete information on side effects

In a subset of infants from 3 placebo-controlled clinical trials (n=6,130 recipients of RotaTeq and 5,560 placebo recipients), RotaTeq was evaluated for all adverse events within 42 days of vaccination with or without concomitant use of other paediatric vaccines. Overall, 47 % of infants given RotaTeq experienced an adverse reaction compared with 45.8 % of infants given placebo. The most commonly reported adverse reactions that occurred more frequently with vaccine than with placebo were pyrexia (20.9 %), diarrhoea (17.6 %) and vomiting (10.1 %). Adverse reactions more common in the vaccine group are listed below per system organ class and frequency. Based on pooled data from 3 clinical trials in which 6,130 infants received RotaTeq and 5,560 received placebo, the adverse reactions listed occurred with excess incidences in RotaTeq recipients compared to placebo recipients of between 0.2 % and 2.5 %.

Infections and infestations

Common: Upper respiratory tract infection

Uncommon: Nasopharyngitis

Gastrointestinal disorders

Very common: Diarrhoea, Vomiting

Uncommon: Abdominal pain upper

Skin and subcutaneous tissue disorders

Uncommon: Rash

General disorders and administration site conditions

Very common: Pyrexia

Intussusception

The risk of intussusception has been evaluated in a placebo-controlled study in infants. During the combined 42-day periods following each dose, there were 6 cases of intussusception in 34,837 recipients of RotaTeq compared with 5 cases in 34,788 placebo recipients.

Post-marketing reports

The following adverse experiences have been spontaneously reported with RotaTeq: haematochezia, urticaria and apnoea in very premature infants (≤ 28 weeks of gestation).

Marketing Authorisation Number:

EU/1/06/348/001

Marketing Authorisation Holder: Sanofi Pasteur

MSD, SNC 8, rue Jonas Salk. F-69007 LYON, France

Rotateq is a registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA

POM

Date of review of prescribing information: June 2009

Table 2: Patient characteristics

Patient characteristic	US GWL	Mammo GWL	p
Age range (yrs)	23-78	36-86	
Mean age (yrs)	44.9 (48)	56.02 (56)	0.009
Mean menarche age (yrs)	12.8	12.43	ns
Premenopausal	2 (48%)*	20 (15.8%)*	0.008
Postmenopausal	13 (52%)*	81 (86.2%)*	0.002
Mean no. of children	1.64	2.05	ns
Mean age of 1st pregnancy (yrs)	20.4 (24)	17.8 (21.5)	ns
Mean age of last pregnancy (yrs)	22.18 (28)	23 (28.5)	ns
No. of patients that breast fed	4 (16%)*	19 (16.8%)*	ns
Breast feeding duration (months)	1-9	2-48	
Oral contraceptive users	5 (20%)*	5 (5%)*	0.02
Range of duration of use (months)	3-120	3-60	
Hormone replacement therapy	1 (4%)*	12 (11.8%)*	ns
Range of duration of use (months)	4-36	3-120	
Smokers	15 (60%)*	13 (12.9%)*	<0.001
Alcohol ingestion	4 (16%)*	7 (6.9%)*	ns
Total abdominal hysterectomy & bilateral salpingo-oophorectomy	2 (8%)*	17 (16.8%)*	ns
Total abdominal hysterectomy only	0	7 (6.9%)*	ns
Bilateral salpingo-oophorectomy only	0	2 (2%)*	ns
Family history of breast cancer	4 (16%)*	32 (31.7%)*	ns
Maternal family history	4 (16%)*	30 (25.7%)*	ns
Paternal family history	0	2 (2%)*	ns
Bilateral family history	0	1 (1%)*	ns
Family history of ovarian cancer	1 (4%)*	2 (2%)*	ns
Family history of colon cancer	0	2 (2%)*	ns

The numbers in brackets are medians. The values in brackets marked with an asterisk represent percentage of that cohort

this cohort of patients had a true positive rate of 16% and a false positive rate of 84%. Figure 3 shows the distribution of the US GWL breast lesions in the different areas of the breast. There were more left sided lesions than right (14 versus 11) and 16 (64%) were located in the upper outer quadrant. Of the 4 US detected breast lesions that were malignant 3 (75%) were located in the upper outer quadrant but this was not statistically significant. Three of these malignant lesions were on the left and the fourth on the right side (Figure 4).

Positive predictive rates and false positive rates

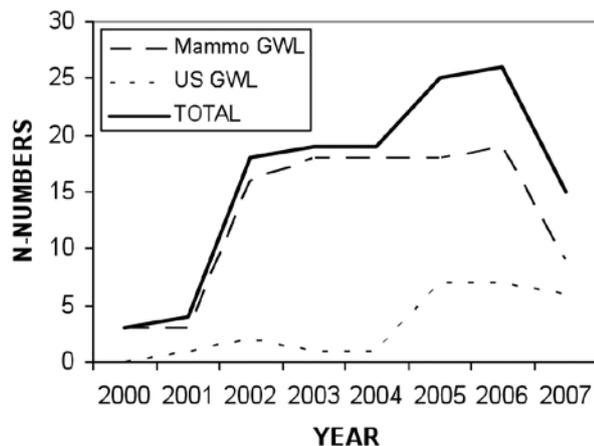
Table 4 shows the positive predictive value (true positive rate) for US and mammographically demonstrable non palpable breast lesions separately and the overall or total results of both modalities together with the 95% confidence intervals. False positive rates as a percentage for the two imaging modalities and the total or overall rate are depicted in Table 5. The chance that a suspicious lesion on US would be benign was estimated

Table 3: Clinical features

	US GWL (n=25)	Mammo GWL (n=101)	p
Breast pain	5 (20%)	5 (4.9%)	0.02
Skin changes	1 (4%)	3 (2.9%)	ns
Palpable breast lump	5 (20%)	8 (7.9%)	ns
Palpable lymph nodes	1 (4%)	1 (0.9%)	ns

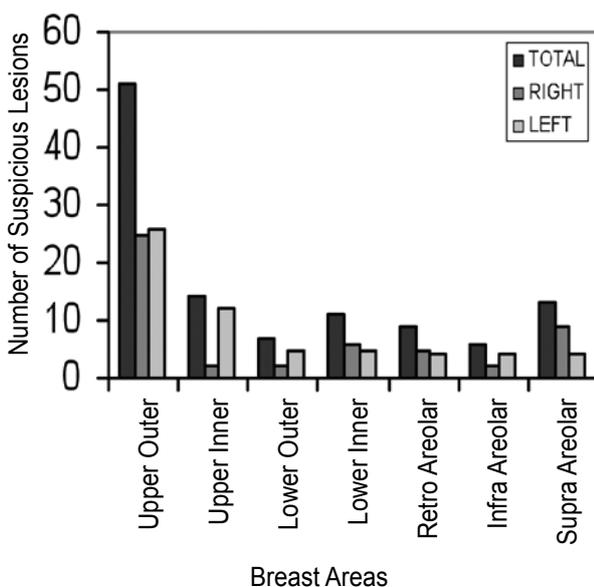
US GWL: ultrasound detected group. Mammo GWL: mammography detected group

Figure 1: Annual Guide Wire Localisations (GWL) for the period 2000-7



US GWL: ultrasound detected group. Mammo GWL: mammography detected group

Figure 2: Distribution of Suspicious Lesions on Mammo GWL



to be 84%, while on mammography this was calculated to be 57.6%, with an overall false positive rate of 62.5%.

Discussion

More than 600,000 women undergo breast biopsies annually worldwide and 20-40% of these are for non palpable breast lesions.¹ Denning et al reported that 20% of non palpable breast lesions are malignant.² Elmore JG et al performed a one year study of breast screening. 23.8% of these women had false positive mammograms.³

Our local cohort had an overall true positive rate of 37.5% and a false positive rate of 62.5%. The latter figure is well above figures in other centres. This is an important issue as a high false positive rate leads to both personal and national economic

Table 4: Positive predicted value for ultrasound and mammography modalities

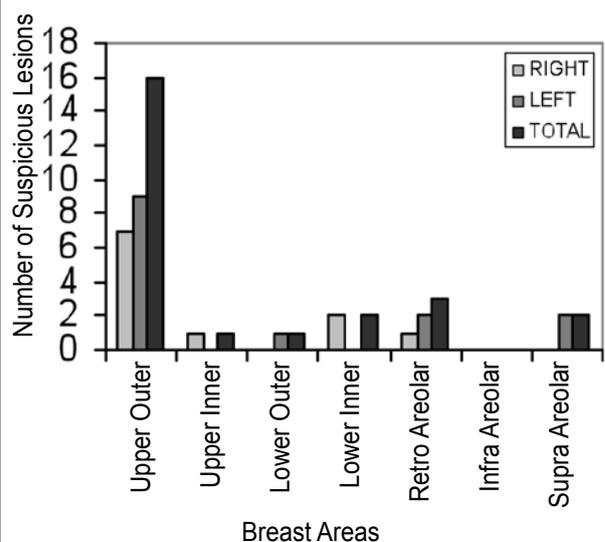
	US	Mammo	Total
Positive predicted value %	16.0	42.3	37.5
LCI	5.3	33.1	29.5
UCI	36.9	52.1	46.2

Table 5: Percentage false positive rate of individual and combined modalities

False positive rate	US GWL	Mammo GWL	Total
%	84	57.6	62.5
LCI	64	48.0	55.0
UCI	95	67.0	72.5

Elmore JG et al reported an average false positive rate in the USA of 23.8% on mammography alone³

Figure 3: Distribution of Suspicious Non Palpable Breast Lesion on US

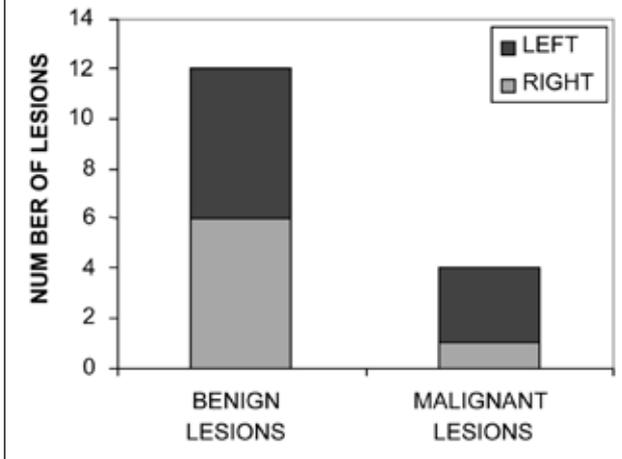


costs, as well as psychological and emotional upheaval. Indeed, a study on 1450 patients who had received a false positive result revealed that these patients were more likely to report feelings of sadness, restlessness and worthlessness.⁴ False positive results may also influence further management of these patients. At best a false positive result may lead to a follow up mammogram. At worst it can lead to a cascade of events ranging from biopsy to mastectomy.

Various studies have shown that both patient dependent and radiologist dependent factors may influence the false positive rate of screen mammograms.

Premenopausal state and young age and history of previous breast biopsy may contribute to increased breast density and may account for uncertainties in reporting. After adjusting for

Figure 4: Distribution of Malignant Lesions versus Benign Lesions in the US GWL group



patient characteristics radiologists have been shown to have a false positive rate ranging from 1.5% to 24.1%.

This inter-radiologist variability was related to inexperience in mammogram interpretation and other unmeasurable factors which accounted for 90% of the between – radiologist variance.⁵

Radiologists who spend more than 20% of their time reading mammograms have a sensitivity of 80% relative to 70% of their peers who spent less time. This is associated with false positive rates of 4.6% and 3.9% respectively.⁶

The number of radiologists working at Mater Dei is below the recommended staff levels and they are not dedicated to breast imaging. This applies to an even greater extent to those working in private clinics. Once a national breast screening programme is introduced there will be the advantage of screening being carried out in a single unit by a dedicated breast team with strict quality control.

Imaging should be done by two dedicated breast radiologists. Improved training in the different breast imaging modalities has also been encouraged in several papers.

The local high false positive rate increases workload, operating times, national health costs and the associated socio-

economic impact. Furthermore, the patient undergoes the procedure under general anaesthesia with associated morbidity and mortality. This raises two important points. The first is that women undergoing screening mammography should be informed of the possibilities of false positive results.

The fact that further invasive or non-invasive tests may be necessary should be made clear to minimise anxiety and to encourage them to undergo further tests if necessary. The awareness of false positivity is also an essential medico-legal issue. The second point is that the introduction of minimally invasive biopsy procedures should be encouraged as these can be done in the imaging department under local anaesthesia and/or minimal sedation on an outpatient basis. Such biopsy procedures are also associated with less breast deformity, lower morbidity, lower costs and minimises on theatre time. With the imminent introduction of stereotactic equipment any woman having a suspicious lesion will avoid an invasive GWL but instead will undergo simply a minimally invasive stereotactic biopsy.

The authors feel that this study is important as it provides a baseline against which the audited results of the recently introduced National Breast Screening Programme can be compared in the future.

References

1. Bloomston M, D'Angelo P, Galliano P, Butler J Jr, Dean R, Rosemurgy AS. One hundred consecutive advanced breast biopsy instrumentation procedures: complications, costs and outcome. *Ann Surg Oncol.* 1999;6: 195-9.
2. Denning DP, Farha GJ, McBoyle MF. Role of needle localization of non palpable breast lesions. *Am J Surg.* 1987; 154:593-6.
3. Elmore JG, Barton MB, Mocerri VM, Polk S, Avene PJ, Fletcher SW. 10 Year risk of false positive screening mammograms and clinical breast examination. *N Engl J Med.* 1998; 338:1089-90.
4. Jatoti I, Zhu K, Shah M, Lawrence W. Psychological distress in US women who have experienced false positive mammograms. *Breast Cancer Res Treat.* 2006;100: 191-200.
5. Tan A, Freeman DH Jr, Goodwin JS, Freeman JL. Variation in false-positive rates of mammography readings among 1067 radiologists: a population based assessment. *Breast Cancer Res Treat.* 2006;100: 309-18.
6. Miglioretti DL, Smith-Bundman R, Abraham L, Brenner RJ, Corney PA, Bowles EJ. Radiologist characteristics associated with interpretive performance of diagnostic mammography. *J Natl Cancer Int.* 2007; 99: 1854-63.