**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.

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**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. 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. 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 ultrasound 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 impalpable 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 χ² 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 a repeat localisation.

Table 1: Guide wire localization: patients and numbers

<table>
<thead>
<tr>
<th></th>
<th>US GWL</th>
<th>Mammo GWL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>25 (19.8%)</td>
<td>101 (80.2%)</td>
<td>126</td>
</tr>
<tr>
<td>GWLs (n)</td>
<td>25 (18.3%)</td>
<td>111 (81.6%)</td>
<td>136</td>
</tr>
</tbody>
</table>

GWL: Guide wire localisations, 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 squeezeable tube (LDPE), with a twist-off cap (HDPE) in a protective bag, pack size of 1
One 2-mI dose contains:
rotavirus serotype* G1 not less than 2 x 10^6 IU1, 2 rotavirus serotype* G2 not less than 2.8 x 10^6 IU, 2 rotavirus serotype* G3 not less than 2.2 x 10^6 IU, 2 rotavirus serotype* G4 not less than 2 x 10^6 IU, 2 rotavirus serotype* P[8] not less than 2.3 x 10^6 IU, 2
1 human-bovine rotavirus reassortants (live), pro-
duced in Vero cells.

1 Infectious Units
2 As lower confidence limit (p = 0.95)

This product contains sucrose 1080 mg

USES:
RotaTeq is indicated for the active im-
munisation of infants from the age of 6 weeks for prevention of gastroenteritis due to rotavirus infec-
tion. In clinical trials, efficacy was demon-
strated against gastroenteritis due to rotavirus serotypes G1P1[8], G2P[4], G3P1[8], 

RotaTeq is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastroenteritis due to 

PRECAUTIONS
No safety or efficacy data are available regard-
ing administration to immunocom-

promised infants, infants infected with HIV or 

Promised 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 re-

cipient (0.3 %) after dose 3. Peak excretion oc-
curred 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 ob-
serve careful hygiene especially when handling 
excreta. In a clinical study, RotaTeq was adminis-
tered 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 gastro-

intestinal illnesses (including chronic diarrhoea) or growth retardation. For the administra-

tion 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 gastroen-

teritis 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 sucrase-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 

(DTαP), Haemophilus influenzae type b vaccine 

(Hib), inactivated poliomyelitis vaccine (IPV), 

Hepatitis B vaccine (HBV) and Pneumococcal 

coccal conjugate vaccine (PCV). Co administration 

of RotaTeq with DTαP-IPV-HBV-Hib vaccine (Infan-

rix 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 sepa-

rate 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 DTαP-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 unaf-

fected. 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: 

DTαP, 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 paediat-

ric vaccines. Overall, 47 % of infants given RotaTeq 

experienced an adverse reaction compared with 

45.8 % of infants given placebo. The most com-

monly reported adverse reactions that occurred 

more frequently with vaccine than with placebo 

were pyrexia (20.9 %), diarrhoea (17.6 %) and vom-

iting (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 recipi-

ents 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

General disorders and administration site condi-

tions

Very common: Pyrexia

Intrususception

The risk of intrususception has been evaluated in 

a placebo-controlled study in infants. During 

the combined 42-day periods following each dose, 

there were 6 cases of intrususception in 34,837 

recipients of RotaTeq compared with 5 cases in 

37,288 placebo recipients.

Post-marketing reports

The following adverse experiences have been 

spontaneously reported with RotaTeq: haemato-

chezia, urticaria and aproxeo 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

Rotateg 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

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

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

Table 3: Clinical features

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>US GWL (n=25)</th>
<th>Mammo GWL (n=101)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast pain</td>
<td>5 (20%)</td>
<td>5 (4.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Skin changes</td>
<td>1 (4%)</td>
<td>3 (2.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Palpable breast lump</td>
<td>5 (20%)</td>
<td>8 (7.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Palpable lymph nodes</td>
<td>1 (4%)</td>
<td>1 (0.9%)</td>
<td>ns</td>
</tr>
</tbody>
</table>


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...
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. Denning et al reported that 20% of non palpable breast lesions are malignant. Elmore JG et al performed a one year study of breast screening. 23.8% of these women had false positive mammograms.

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 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. 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.

Table 4: Positive predicted value for ultrasound and mammography modalities

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Mammo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predicted value %</td>
<td>16.0</td>
<td>42.3</td>
<td>37.5</td>
</tr>
<tr>
<td>LCI</td>
<td>5.3</td>
<td>33.1</td>
<td>29.5</td>
</tr>
<tr>
<td>UCI</td>
<td>36.9</td>
<td>52.1</td>
<td>46.2</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>US GWL</th>
<th>Mammo GWL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>84</td>
<td>57.6</td>
<td>62.5</td>
</tr>
<tr>
<td>LCI</td>
<td>64</td>
<td>48.0</td>
<td>55.0</td>
</tr>
<tr>
<td>UCI</td>
<td>95</td>
<td>67.0</td>
<td>72.5</td>
</tr>
</tbody>
</table>

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

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