THE PATHOLOGIST INPUT IN A ONE STOP CLINIC FOR BREAST LESIONS

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Conflict of interest: no disclosure
CONTEXT IN 2004

- French breast cancer screening program launched and efficient, **BUT**:  
  - Post-screening care: not organized  
  - Surgical delays: twice as expected and recommended (3 months instead of 1 month)

- Evolution of breast care towards non palpable lesions: importance of a close collaboration between clinicians, radiologists and (cyto)pathologists
French & European recommendations

- **Preoperative diagnosis of breast lesions**: mandatory

- **Delay between first screening test and surgery**: ≤ 1 month for breast cancer

- **Preoperative multidisciplinary assessment**: mandatory in most cases

- **Postoperative multidisciplinary assessment**: mandatory
Objectives

- **Be quick**: reduce diagnostic delays
- **Multi-disciplinarity**: immediate
- **Humanity** and multiprofessional care
- **Efficiency**: medical & health economic
- **Early integration** of clinical and biological research
ORGANIZATION OF THE ONE-STOP CLINIC

Phone call

Radiologist  Surgeon  Oncologist  Pathologist

Total agreement

No agreement or no diagnosis

Appropriate treatment or follow up as required

Go further

Immediate diagnosis as frequent as possible

Shared diagnosis and decision
Phone call

direct patients to the most appropriate medical visit

Information sheet sent to the patient
Phone call

Diagnosis of cancer

- Already treated or advice only
- Tumor < 3 cm
- Large tumor or emergency

No diagnosis

- Calcifications only
- Tumor < 3 cm
- Large tumor or emergency

Advice on medical records

Surgeon

Oncologist

Radiologist

Surgeon

Oncologist
Main actors

1.5 surgeons  1.2 oncologists  2 radiologists  1 cytopathologist

1.0 nurse (coordination)  
1.2 nurse  
1.5 technician (pathology)  
1.5 technician (imaging)  
1.0 person (patients’ reception)  
3.0 medical secretaries

35 patients in a day once a week
Typical itinerary 1: subclinical mass

PATIENT ARRIVES IN THE UNIT

VISIT OF THE FIRST SPECIALIST

REVIEW OF PREVIOUS IMAGING, CONCERTED DECISION

COMPLEMENTARY MAMMOGRAM AND/OR US

US-GUIDED FNA

LUNCH

RESULTS AT BACK VISIT TO THE FIRST SPECIALIST

VISIT OF SURGEON

PATIENT LEAVES WITH ALL SURGICAL APPOINTMENTS
BLOOD TESTS, FIRST EXTENSION ASSESSMENTS
FNA + CORE BIOPSY + FROZEN SAMPLE
BLOOD TESTS, FIRST EXTENSION ASSESSMENTS
LUNCH
RESULTS AT BACK VISIT TO THE ONCOLOGIST
PATIENT LEAVES WITH APPOINTMENTS FOR MEDICAL ONCOLOGIST VISIT AND CHEMOTHERAPY
Typical itinerary 3: calcifications

PATIENT ARRIVES IN THE UNIT

VISIT OF FIRST SPECIALIST
Explanations on breast lesions, the diagnostic procedure, potential diagnostics and implications

REVIEW OF PREVIOUS IMAGING
Concerted decision

STEREOTACTIC MACROBIOPSY

PATIENT LEAVES WITH MEDICAL AND SURGICAL APPOINTMENTS
Multidisciplinary approach
Perfect concordance is mandatory

Clinician  Radiologist  Pathologist

DIAGNOSTIC CONCORDANCE

Multidisciplinarity +++
A single discordant finding: go further +++
**Decision tree**

**Birad 4**
- FNA benign
  - Biopsy
    - benign
      - Follow up
    - cancer
- FNA cancer
- Biopsy if mastectomy or primary medical trt

**Birad 5**
- FNA cancer
  - Surgery
- FNA other
  - Biopsy
    - But exceptional documented cases
  - Surgery
  - Surgery
FNA of nodules

Several successive evaluations

Median age: 56 yrs

Median lesion size: 15 mm
FNA: results

As a mean on several successive evaluations from a total of >7000 FNA

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory specimens</td>
<td>2%</td>
</tr>
<tr>
<td>Suspect</td>
<td>8%</td>
</tr>
<tr>
<td>Cancer</td>
<td>55%</td>
</tr>
<tr>
<td>Benign</td>
<td>35%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fx positive</td>
<td>0.1%</td>
</tr>
<tr>
<td>Fx negative</td>
<td>3%</td>
</tr>
</tbody>
</table>
Needs, requirements, and potential problems

- Need of well-trained senior physicians
- Sophisticated organisation
- Trust in the other doctors of the team
- Modesty and team spirit mandatory
- Necessity of a permanent quality control
- Diagnoses given too rapidly?
Patient’s satisfaction

90% overall satisfied
In summary the main advantages are:

- **Systematic review** of images by radiologist: multifocality evidenced in some cases
- **Multidisciplinary approach**
- Early initiation of general work-up
- **Screening for inclusion in national and international clinical trials** (imaging, surgery, neoadjuvant chemo/hormone therapy)
- **Banking** of samples with patient’s written informed consent (leftovers) for translational research activities
RESEARCH ASPECTS

- Imaging: contrast doppler, angio-mammography, tomosynthesis, optic imaging...
- Psychocognitive
- Health economics
- Translational research
### Health economics

697 FNA among 670 successive patients

<table>
<thead>
<tr>
<th>Patient and lesion characteristics</th>
<th>N = 670 pts</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>56 (16-92)</td>
<td></td>
</tr>
<tr>
<td>Menopausal</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Palpable lesion</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Median relative risk (Gail model)</td>
<td>1.61</td>
<td></td>
</tr>
<tr>
<td>Median lesion size (mm)</td>
<td>15 (2-150)</td>
<td></td>
</tr>
<tr>
<td>US-guided FNA</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Birad ACR classification of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birad 2</td>
<td>14 (2%)</td>
<td></td>
</tr>
<tr>
<td>Birad 3</td>
<td>156 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>Birad 4</td>
<td>172 (24.7%)</td>
<td></td>
</tr>
</tbody>
</table>
# Indices of diagnostic performance

<table>
<thead>
<tr>
<th></th>
<th>FNA*</th>
<th>One stop unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.84%</td>
<td>97.16%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.07%</td>
<td>99.20%</td>
</tr>
<tr>
<td>Efficacy</td>
<td>98.80%</td>
<td>92.40%</td>
</tr>
<tr>
<td>Youden index</td>
<td>0.959</td>
<td>0.963</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>104.129</td>
<td>121.450</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.032</td>
<td>0.029</td>
</tr>
<tr>
<td>PPV</td>
<td>99.46%</td>
<td>92.98%</td>
</tr>
<tr>
<td>NPV</td>
<td>94.69%</td>
<td>90.80%</td>
</tr>
</tbody>
</table>

* Does not take into account the suspicious and unclassified lesions
## Cytological diagnosis

697 FNA among 670 successive patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>370 (53.08)</td>
</tr>
<tr>
<td>Benign</td>
<td>247 (35.44)</td>
</tr>
<tr>
<td>Suspicious</td>
<td>59 (8.46)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>21 (3.01)</td>
</tr>
</tbody>
</table>
Mesure of direct costs

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Median</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA for palpable lesion</td>
<td>11 €</td>
<td>7.5 - 21.17 €</td>
</tr>
<tr>
<td>US-guided FNA</td>
<td>27 €</td>
<td>18.75 - 45.30 €</td>
</tr>
<tr>
<td>US-guided biopsy</td>
<td>185 €</td>
<td>157.11 - 237.91 €</td>
</tr>
</tbody>
</table>
Overall cost for the 697 lesions (670 patients) for an exact diagnosis, including biopsies and surgeries where necessary: 56,463 €

Overall cost if 697 biopsies had been used with no false positive or false negative result: 123,950 €
In summary

- Efficacy results were comparable to the best results published in the literature.
- FNA has an equivalent specificity but a slightly lower sensitivity than US-guided biopsy and therefore shall always be used in a cautious multidisciplinary approach, which is able to provide excellent results.
- In this setting, FNA appears as very a cost-effective diagnostic tool for the rapid diagnosis of breast lesions in a one stop multidisciplinary breast unit.
Benign or malignant?
Development of diagnostic biomarkers:

- based on molecular tools and
- applicable to breast FNA
Qualitative & quantitative RNA yield?

144 FNA
↓
114 mRNA with adequate quantity
↓
111 samples with >1μg mRNA (97%)
↓
109 samples evaluated for quality (RIN)
↓
97 OK for arrays (89%)

Median RIN of all samples: 7.5 (1.7-9.5)
Correlation between ER levels assessed by PCR and IHC

Correlation: 94%

Correlation between HER2 levels assessed by PCR and IHC (± FISH)

Correlation: 98%

Identifying biomarkers of diagnosis

- Gene expression arrays have generated molecular predictors of relapse and drug sensitivity

- Aim:
  - identify exons differently expressed in malignant and benign breast lesions, and
  - build a molecular classifier for breast cancer cytodiagnosis by means of splice array
Alternative RNA splicing

Genomic DNA → Pre-messenger RNA → messenger RNA → Proteome

Exon 1 Exon 2 Exon 3 Exon 4 Exon 5

RNA Splicing

A

Function A

B

Function B

Transcription

Unprocessed Transcriptome

Transcriptome

Genome

New protein structure and function
- Affects signaling pathways
- Modifies drug efficacy
Results using a splicing array chip technology

- 165 breast FNA: 120 malignant and 45 benign lesions
- Training set (n=94), validation set (n=71)
- A molecular classifier with 1228 probe sets was generated from the training set of 94 FNA
- This signature accurately classified all samples (accuracy=100%; 95% CI: 96-100%)
- The molecular predictor accurately classified 68 of 71 lesions in the validation set of 71 FNA (accuracy=96%; 95% CI: 88-99%)
Correlation of each specimen with the average benign and malignant profiles

Figure 2: Correlation of each specimen with the average benign and malignant profiles
(A) Specimens from the training set during the leave-one-out cross-validation procedure. (B) Specimens from the validation set.
Conclusions of our study

- Many exons are differentially expressed in breast cancer as compared with breast benign lesions
- These alternative transcripts are detectable on material obtained by FNA
- Using this type of approach may contribute to increase sensitivity and specificity of breast cancer cytodiagnosis

Diagnostic test

Fine Needle Aspirate (less than 1 min)

Total RNA extraction (< 2 hours)

RNA qualification (< 30 min)

Diagnostic result

RNA amplification (< 7 hours)

Affymetrix Gene Chip station (washes, staining and scanning) (< 4 hours)

Hybridisation (16 hours)

Fragmentation and labelling (< 2.5 hours)

40% of biopsy
Benign or malignant?
Perspectives using molecular cytopathology

One stop clinic: breast, thyroid, other tumors

FNAC

Morphological result day 1

Molecular characterization for diagnostic, prognostic and predictive purposes

Molecular results within 1 week
L’équipe d’accueil en Pathologie mammaire

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