Point-of-Care technologies for cervical cancer screening

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UNC Global Women’s Health
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Leading cause of cancer death in women – by country (2018)
Lifetime Risk of Cervical Cancer in South Africa

Black women
26 PER 100,000

White women
15 PER 100,000

WHO 2014
Rationale for point-of-care HPV screening

- In randomized trials, HPV screening predicts cervical disease better than VIA or cytology
- The availability of POC molecular testing may expand access to cervical screening through HPV “test-and-treat” strategies
- HPV self-testing may also improve cervical screening coverage

Denny 2005; Sankar 2009; Kuhn, 2010; Ronco, 2014
Methods

• 3 performance validation studies
  • Zambia (CCRCI)
    – 200 HIV-infected women
    – Xpert HPV, OncoE6, VIA, and DC compared to histology
  • South Africa (VICAR)
    – 1,161 HIV-infected women
    – Xpert HPV and Hybrid Capture II compared to histology
  • South Africa (VHX)
    – 350 HIV-infected women
    – Agreement between self- and provider-collected Xpert HPV
**Xpert HPV**
- Qualitative real-time PCR
- Detects 14 hrHPV types
- 1 hour runtime

**OncoE6**
- Oncoprotein lateral flow test
- Detects E6 from 2 hrHPV types
- 1.5 hour runtime
Results: CCRCI

![Pie chart showing test results]

Clinical Performance Using CIN2+

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert HPV</td>
<td>88 (71-97)</td>
<td>60 (52-68)</td>
</tr>
<tr>
<td>OncoE6</td>
<td>31 (16-50)</td>
<td>99 (97-100)</td>
</tr>
<tr>
<td>VIA</td>
<td>48 (30-67)</td>
<td>92 (86-95)</td>
</tr>
<tr>
<td>DC</td>
<td>59 (41-76)</td>
<td>88 (82-93)</td>
</tr>
</tbody>
</table>

Chibwesha, 2016
## Results: VICAR

### Clinical Performance Using CIN2+

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hybrid Capture II</td>
<td>92 (87-96)</td>
<td>51 (48-55)</td>
<td>42 (38-46)</td>
<td>94 (91-97)</td>
</tr>
<tr>
<td>Any Xpert HPV</td>
<td>88 (84-93)</td>
<td>48 (45-52)</td>
<td>40 (37-44)</td>
<td>91 (88-95)</td>
</tr>
</tbody>
</table>

Mbulawa, 2016
## Results: VHX

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Self</th>
<th>Provider</th>
<th>Kappa (95% CI)</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hrHPV</td>
<td>45%</td>
<td>37%</td>
<td>0.65 (0.52-0.77)</td>
<td>83%</td>
</tr>
<tr>
<td>HPV16</td>
<td>8%</td>
<td>6%</td>
<td>0.74 (0.53-0.96)</td>
<td>97%</td>
</tr>
<tr>
<td>HPV18/45</td>
<td>12%</td>
<td>8%</td>
<td>0.69 (0.48-0.89)</td>
<td>95%</td>
</tr>
<tr>
<td>HPV31/33/35/52/58</td>
<td>26%</td>
<td>20%</td>
<td>0.66 (0.51-0.80)</td>
<td>88%</td>
</tr>
<tr>
<td>HPV51/59</td>
<td>8%</td>
<td>6%</td>
<td>0.61 (0.34-0.87)</td>
<td>96%</td>
</tr>
<tr>
<td>HPV39/68/56/66</td>
<td>18%</td>
<td>15%</td>
<td>0.80 (0.67-0.93)</td>
<td>95%</td>
</tr>
</tbody>
</table>
Conclusions

• POC testing circumvents the logistic and operational barriers associated with traditional, off-site laboratory testing
• Our validation studies confirm that Xpert HPV performs equivalently to current FDA-approved HPV tests
• We also observed robust agreement between self- and provider-collected Xpert samples, suggesting a role for self-testing in future HPV test-and-treat programs
Future Directions

- Larger trials and programs are needed to explore optimal implementation strategies for POC technologies, including:
  - HPV screening followed by triage with VIA, cytology, and/or colposcopy
  - Approaches that include same-day treatment
  - The role of mHealth solutions
- Cost-effectiveness analyses are also needed
Acknowledgements
GE Oncology

Claire Goodliffe
Global Oncology Director

One Stop Breast Clinic

Accelerating access to diagnosis & treatment
GE Oncology

- Provide technology, solutions and service so clinicians can make better decisions for their patients.
- Help make patients cancer care journey more efficient and personalized.

GEHC Businesses
- 11 Imaging Businesses
  - Surgery & Interventional
  - Radiotherapy Planning
Centricity MDT
Cell Therapy
Bioprocessing
GE Partners
Global Design
Service

Projects
- One Stop Clinic
- The Symptomatic Clinic
- Carepathway Management

Research
- Imaging
- CAR T Therapy
- Treatment Monitoring
- Patient Behavior
- Risk Assessments
- Clinicians Practice Behavior

Partners
- Pharma
- Scientific Societies
- Charities
- Governments
- Cancer Hospitals
Delays in diagnosis and treatment

The low survival rates in developing countries are explained by scarcity of early detection programs, resulting in a high proportion of women presenting with late-stage disease at diagnosis, along with the lack of adequate diagnosis and treatment facilities.
Gustave Roussy

The premier European Cancer Centre – Villejuif France.

Centre for patient care, research and teaching, and patients with all types of cancer

The first dedicated One Stop Breast Clinic in France

3 500 employees
545 doctors
1400 nursing staff
450 researchers
One Stop Breast Clinic

Diagnostic Breast Cancer Clinic for women with signs or symptoms of Breast Cancer.

Designed by Dr. S. Delalogue and team in 2004 to receive women from the French screening program.

Organized and efficient care pathway that fosters same day diagnosis

19,000 women have been treated at the clinic since 2004

1. The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137
GE Healthcare sponsored the data mining of the breast clinic in 2012.

The analysis confirmed the clinic diagnosed 75% of patients the same day.

Oxford Analytica confirmed Gustave Roussy’s findings.

One Stop Clinic breast study published in *European Journal of Cancer* 2016.
One Stop Breast Clinic

Clinic Objectives

- Improve quality of diagnoses
- Reduce time intervals to render diagnoses
- Lower costs of the complete procedures
- Improve patients’ satisfaction
- Improve pain management
- Reduce patients’ anxiety
- Improve patients’ information for recalls
Clinical Triage of Patients

- Patients referred to breast center for suspect lesions (BI-RADS 3,4,5)
- All patients with solid tumors receive FNA to rule out benign lesions and detect malignancy
- Microcalcifications are biopsied with sterotaxy and those patients receive a diagnosis on another day during the week
- Malignant patients have core biopsies at lumpectomy or surgery

Multidisciplinary Team Members

| 3 Radiologists |
| 1 Breast Surgeon |
| 1 Oncologist |
| 1 Cytologist |

| 1 coordination nurse |
| 1 pathology technician |
| 1,2 nurse |
| 1,5 imaging technician |
| 1 person to welcome patients |
| 3 medical assistants |
Clinical and Economic Outcomes

- 75% of patients have their results on the same day.\(^1\)
- 96% of FNA patients were able to leave with a diagnosis the same day.
- Sensitivity 97.2% & specificity: 99.7% \(^1\).
- Biopsies avoided in 10% of all patients who underwent a CESM \(^1\).
- Up to 50% reduced total cost per patient for benign cases and by 33% of costs for malignant cases. \(^1\)
- Patients very satisfied with the one-day diagnosis. \(^1\)

\(^1\) The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137
One Stop Breast Clinic

Identification of Pilot Sites

Gustave Roussy and GE Healthcare developed a partnership

Set up pilot clinics in countries that would benefit the most from diagnosis in the same day.

GE evaluated pilot sites:
- Colombia
- Mexico
- Algeria
- Kenya

Medellin
- Screening population of 123,000 women
- Serve 62% of screening population
- Projected 5000 patients with BIRADS 4 & 5

1. The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137
One Stop Clinic adapted to Medellin, Colombia

Assessment of the sites and care pathways with Multidisciplinary Team

Project teams @
- Dinamica
- Gustave Roussy
- GE Healthcare

Gustave Roussy visit Medellin to meet the team and assess clinics.

Visit of multidisciplinary team from Medellin to meet Gustave Roussy team

Training on organizational and clinical algorithms

One Stop Clinic opens at the INCODOL hospital

Multidisciplinary team
- 4 Days a week
- 12 pts per day
- 4 Defined care pathways
- 2 month Trial period
4 Carepathways

- **Patients**: 15 per day
- **Staff**: Nurse – radiologist – pathologist, mastologist – healthcare personnel
- **Education**: GPs training via webex, Telemarketing to patients, Dedicated web site
- **Cost**: 7-30$ HMO subsidizes 80% of the co-pay
Learnings

- Assessment of the pilot sites. **Follow the patient journey**
- Clinical pathways are **reasonable and achievable**
- Training needs - **make everyone feel comfortable**
- Stakeholder buy in and lock down with contracts
- **Small and skilled** project team
- Run the project like a business
- Financial support and governance
- **Be ready to pivot** if you face barriers
- **Embrace diplomacy and empathy**

*Keep the patient at the centre of your goals*
GE Oncology

Fostering best practices between institutions to improve access to diagnosis and treatment

New Projects

• Clinic for post-treatment cancer patients & survivors
• Accelerating time to brain cancer diagnosis
Role of technological advances in breast cancer early detection in limited resource settings

R. Sankaranarayanan MD

Senior Visiting Scientist, WHO-IARC, Lyon, France
Senior Medical Advisor, RTI International-India
Former Special Advisor on Cancer Control and Former Head of Early Detection & Prevention Section, WHO-IARC, Lyon, France

Conflicts of Interest: None
Point-of-care testing: what it means?

• *An investigation done at the time of the consultation with instant availability of results to make immediate and informed decisions about patient care*

• *The intention is to perform diagnosis and treatment in the fastest time frame*

• *Done at homes, clinics, doctors offices, primary care settings, hospitals, emergency services, field settings*

Early detection of cancer: two major strategies

- Screening programs: targets asymptomatic people
- Early diagnosis: targets in symptomatic patients
- Population and health provider awareness as well as adequately developed health systems are critical for both the above approaches
Early diagnosis

- Targets symptomatic people
- Prompt symptom recognition and physical examination are critical
- Awareness among people and general practitioners and primary care physicians is vital
- Prompt referral and investigations are vital
The utility of different early detection tests in breast cancer early detection

<table>
<thead>
<tr>
<th>Early detection test</th>
<th>Screening programs</th>
<th>Early diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen film mammography</td>
<td>Routinely used (screening mammography)</td>
<td>Routinely used (diagnostic mammography)</td>
</tr>
<tr>
<td>Digital mammography</td>
<td>Routinely used (screening mammography)</td>
<td>Routinely used (diagnostic mammography)</td>
</tr>
<tr>
<td>Digital breast tomosynthesis</td>
<td>No defined role</td>
<td>In selected situations mostly in high income countries</td>
</tr>
<tr>
<td>Computer assisted detection</td>
<td>Useful in selected situations</td>
<td>Clinical data absent</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Not as a primary screening tool, but adjunctive to mammography</td>
<td>Routinely used</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>No defined role</td>
<td>Useful in selected situations such as high risk women with BRCA mutations, 20% or more lifetime risk</td>
</tr>
<tr>
<td>Positron emission tomography</td>
<td>No role</td>
<td>Clinical data absent; not used</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td>Useful adjunctive to mammography/ultrasonography</td>
<td>Routinely used</td>
</tr>
<tr>
<td>Breast self- examination</td>
<td>May facilitate participation in screening programs</td>
<td>May facilitate early diagnosis</td>
</tr>
<tr>
<td>Breast awareness</td>
<td>May facilitate participation in screening programs</td>
<td>May facilitate early diagnosis</td>
</tr>
</tbody>
</table>
Point of care testing technologies being evaluated for early detection of breast cancer

- Clinical breast examination
- Handheld, portable, rechargeable battery powered and low cost ultrasound
- Automated ultrasound
- Breast elastography
- Optical imaging technologies using near infrared light
- Fine needle aspiration cytology supported by computer assisted detection using artificial intelligence
Physical examination of the breast

- Breast cancers ≤2 cm dimension can be readily detected by physical examination of the breast.
- A palpable lump prompts referral for further assessment.
iBreastExam device
iBreast examination

- iBreastExam's sensors assess and identify tissue elasticity differences between hard and stiff breast tumour tissue compared to normal breast tissue.
- The tactile sensor technology using Piezoelectric Sensor Array is a novel, quantitative and low-cost elastic modulus (E) sensor that can measure tissue compression and stiffness by top down touching of the skin surface.
- iBE’s ability to apply a gentle force and measure the subtle displacements electrically, all within the sensor, provides ‘electronic palpation’ sensor for in-vivo breast imaging.
Portable, handheld ultrasound for breast cancer early detection

- Hardware modifications to improve portability, enhance simplicity of use, and reduce cost have helped promote the use of ultrasound devices in LMICs.

- There are now several products in the market that have taken such considerations into account with promising results, demonstrating the feasibility of using compact, portable ultrasound in primary care and can be used by healthcare workers with a range of training levels.

- Sensivity: 74-91%; Specificity 72-96%; PPV: 3-32%.

- The low-cost ultrasound hardware has prompted the development of pathology-driven, clinically applicable image analysis software such as computer-aided detection and diagnosis (CADD).

Ref: Thigpen D et al., Diagnostics 2018; 8: 20
Portable, handheld ultrasound for breast cancer early detection: challenges and limitations

- Handheld screening ultrasound, requires a great deal of resources to screen large numbers of women as the scanning is performed by the technologist.

- The identification of the sonographically detected abnormality is made by the technologist, making it operator dependent.

- The time, required for a bilateral handheld whole breast ultrasound, can range from 15 - 20 min, making it challenging to implement in a clinical practice

Ref: Thigpen D et al., Diagnostics 2018; 8: 20
Automated ultrasound for breast cancer early detection

• Automated whole breast ultrasound allows for uncoupling of image acquisition from interpretation.

• The entirety of the breast can be imaged and subsequently the entire data set can be reviewed by the radiologist.

• Allows for more reliable and reproducible imaging of the entirety of the breast

• Allows the radiologist to interpret the entire data set as opposed to representative images obtained by a technologist.

• Image acquisition takes 60 s per view with a total examination time of about 15 minutes. Study interpretation time, performed by the radiologist is around 3 minutes

Ref: Thigpen D et al., Diagnostics 2018; 8: 20
Breast elastography

- Breast elastography is a sonographic imaging technique which provides a non-invasive evaluation of the stiffness of a lesion.
- It combines US technology with US elastography which noninvasively assesses tissue deformability by providing information on the elasticity. It is based on the premise that there are significant differences in the mechanical properties of tissues that can be detected by applying an external mechanical force.
- Two technical solutions are available for clinical use: strain elastography (real time elastography) and shear wave elastography.
- They may substantially improve differentiating between benign and malignant breast lesions thereby limiting recourse to biopsy and considerably reducing the number of benign breast biopsy diagnoses.

Ref: Goddi et al., Journal of Ultrasound 2012; 15, 192-198
https://appliedradiology.com/articles/breast-elastography-a-new-paradigm-in-diagnostic-breast-imaging
Real time elastography (RTE): Advantages and disadvantages

• Short examination time required, real-time display, immediate interpretation and limited cost, and the criteria adopted in the image interpretation have proven to be adequate in clinical practice.

• It is an exclusively qualitative method influenced by histotype and lesion size; is an operator dependent technique which requires special training, and the use of semi-quantitative indices does not improve the performance of the method and does not reduce interoperator variability
Breast elastography: A new paradigm in diagnostic breast imaging

Source: https://appliedradiology.com/articles/breast-elastography-a-new-paradigm-in-diagnostic-breast-imaging
Shear Wave Elastography

- The limitations of RTE can be compensated by shear wave elastography, which is a quantitative method providing a more accurate assessment of the spatial distribution of tissue stiffness.
- Shear wave elastography has limitations such as the difficulty in measuring shear wave velocity in very stiff breast lesions. In this type of tumors real-time elastography has demonstrated a high sensitivity which can compensate for the limitations of shear wave elastography.
- Both RTE and shear wave elastography should be combined to overcome the limitations of both.
A 42-year-old woman with a pathologically proven invasive ductal carcinoma. A freehand region of interest was drawn manually by tracing the border of the mass using shear-wave elastography to measure lesion elasticity.

Youk et al, Ultrasonography 2017;36:300-309Shear. https://doi.org/10.14366/usg.17024
Side-by-side display of anatomical B-mode US image (left) and overlaid color map of simultaneous shear wave measurements (right) of a breast lesion obtained with 2D-SWE on a SuperSonic Imagine (SSI) AixplorerTM. In this system, red color represents stiff tissue and blue color reflects soft tissue. The suspicious hypoechoic lesion (shown within rectangle on B-mode image) has an irregular border, angular margins, is slightly wider than tall and shows posterior acoustic shadowing. The elastogram suggested malignant etiology due to increased stiffness (red/yellow/green) and ductal adenocarcinoma was confirmed on subsequent biopsy. Image courtesy by Dr. Osmar Saito.

Sigrist et al., Theranostics 2017; 7(5): 1303-1329. doi: 10.7150/thno.18650
Breast awareness for women

• Each woman knowing what is normal for her
• Being aware of breast cancer symptoms/signs/risk factors
• Being aware of high survival/cure rates and quality of life if detected and treated early
• Undergoing periodic breast inspection and palpation
• Seeking prompt medical attention if any abnormality suspected
Breast awareness for doctors and nurses

• Knowing about breast cancer!
• Knowing about breast cancer signs and symptoms!
• Knowing about the differential diagnosis of different breast signs and symptoms!
• Knowing the art of clinical suspicious and prompt referral!
• Knowing how to counsel!
<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>&lt;25 years</th>
<th>25-35 years</th>
<th>35-55 years</th>
<th>&gt;55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile lump (single)</td>
<td>Fibroadenoma</td>
<td>Fibroadenoma</td>
<td>Fibroadenoma</td>
<td>Phyllloides</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phyllloides tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tumour</td>
<td></td>
</tr>
<tr>
<td>Ill defined lump/s or lumpy areas or feel-cyclic pain</td>
<td>Uncommon</td>
<td>Fibrocystic disease/ Sclerosing adenosis</td>
<td>Fibrocystic disease</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Firm lump/hard lump/fixed lump/skin tethering</td>
<td>Uncommon</td>
<td>Carcinoma</td>
<td>Carcinoma</td>
<td>Carcinoma/Fat necrosis</td>
</tr>
<tr>
<td>Nipple ulceration, eczema</td>
<td>Nipple adenoma</td>
<td>Nipple adenoma</td>
<td>Paget’s disease/ Nipple adenoma</td>
<td>Paget’s disease/ Nipple adenoma</td>
</tr>
<tr>
<td>Bloody nipple discharge</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Duct papilloma/ In situ carcinoma</td>
<td>Duct papilloma/ In situ carcinoma</td>
</tr>
<tr>
<td>Clear discharge/pus</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Duct ectasia</td>
<td>Duct ectasia</td>
</tr>
<tr>
<td>Breast sign/symptom and likely differential diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------------------</td>
<td></td>
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<tr>
<td>Lump</td>
<td>Clinical suspicion</td>
<td></td>
<td></td>
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<tr>
<td>Diffuse</td>
<td>Fibroadenosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Discrete or tethered</td>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobile</td>
<td>Benign tumour, most likely fibroadenoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin features</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Oedema (peau de orange)/puckering/tethering</td>
<td>Cancer</td>
<td></td>
<td></td>
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<tr>
<td>Erythema</td>
<td>Inflammation/Cancer</td>
<td></td>
<td></td>
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<tr>
<td>Nipple</td>
<td></td>
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<tr>
<td>Milky discharge</td>
<td>Pregnancy/prolactinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/green discharge</td>
<td>Duct ectasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloody discharge</td>
<td>Duct papilloma/rarely cancer</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Retraction/scaling/erythema/eczema</td>
<td>Paget’s disease of nipple/carcinoma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breast Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclical</td>
<td>Fibroadenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On palpation</td>
<td>Mastitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent, local, non-cyclical, constant</td>
<td>Cancer</td>
<td></td>
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</tr>
</tbody>
</table>
Early diagnosis of breast cancer: triple diagnosis

• Physical examination (clinical assessment)

• Diagnostic imaging (mammography/ultrasonography)

• Tissue sampling (FNAC/core biopsy/excision biopsy/frozen section)

• Excellent sensitivity (99%) and specificity (99%)
5-year survival from breast cancer in the Cancer Institute (WIA), a tertiary care centre in Chennai, India, during 1967-2006

<table>
<thead>
<tr>
<th>Stage</th>
<th>Before the introduction of adjuvant treatments</th>
<th>After introduction of adjuvant hormone and chemotherapy treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (N=169)</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>II (N=2624)</td>
<td>62%</td>
<td>78%</td>
</tr>
<tr>
<td>III (N=4496)</td>
<td>34%</td>
<td>43%</td>
</tr>
<tr>
<td>IV (N=1042)</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>All stages (N=10 411)</td>
<td>39%</td>
<td>49%</td>
</tr>
</tbody>
</table>