GOSTT in Breast Cancer

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Outline

• Breast ca
• SLN Detection
• ROLL & SNOLL
• Intraoperative imaging & GOSST
• Literature & New horizons
GOSST in Breast Ca

“Breast ca is still as scary as a GHOST...”
Breast Ca... Scary as a Ghost

- Most common cancer in female gender
- Most fatal ca among 40-55 year-old women
- Lifelong risk for women: 12.3%
- 1 in every 8 women has risk to develop breast ca

Smith et al, CA Cancer J Clinic 2003
GOSST in Breast Ca

Breast ca may be hard-to-be visualised as a GHOST...”
Breast cancer is hard-to-be visualised

- Breast cancer < 15 mm in 54% of all invasive cancer
- 5/1000 women have invasive cancer

- Non-palpable lesions...”ghost“ lesions
- Incidence: 17%-58%

Markopoulos, World J Surg 1999
Winchester, Surg Clin North America 1996
• Lymph node metastasis is an important prognostic factor

• Sentinel lymph node concept is part of standard routine care in invasive breast ca
Sentinel Lymph Node (SLN)

The first lymph node that drains the tumor
SLN

Theoretical Basis

• Histopathology of SLN reflects histopathology of lymphatic basin...
Breast Ca & SLN Detection

- Less invasive
- Reflects axillary Histopathology
- Cost effective
- Easily applied
History

Gray, 1930’s: “Lymph nodes are the first and most probable place for metastasis”

- Ramon Cabanas, 1977: “SLN concept in penile ca”
- Morton 1992: “SLN detection by blue dye in M.melanoma”
- Giuliano et al, 1994: “SLN in breast ca”
- Krag et al, 1993: “First gamma probe”
Lymphatic mapping and Sentinel Lymphadenectomy

“Sentinel Node localization is the second most important development in this century after conservative lumpectomy for the treatment of early breast cancer”

Hiram S. Cody III, MD, January 1989
Department of Surgery,
Memorial Sloan-Kettering Cancer Center
SLN Detection-Radioguided Surgery (Conventional way)

- Blue dye ............ Blue lymph nodes (visual)
- Scintigraphy ...... hot spots (visual)
- Gamma probe ... sound signals (audio)

- Blue dye + Scintigraphy + Gamma Probe
- (Audio-visual)
Radioguided Surgery-Why?

• Less invasive evolution of oncologic surgery
• Less operation duration & complications
• Significance of SLN concept & N staging
• Targeted tumor / lesion picking trend
• Laparoscopic surgery
• Robotic surgery
• ...
Breast Ca & SLN

- No axillary LN met in 70-80% early stage
- Unnecessary axillary dissection
- Morbidity
Complications of Axillary Dissection

- Paresthesia (50-70%)
- Pain (30-40%)
- Weakness (25%)
- Lymphoedema (10-15%)
- Infection (5-10%)
- Shoulder dysfunction (17%)
- Seroma
RGS & Immunohistochemistry

H&E

Immunohistochemistry
## SLN Detection:

<table>
<thead>
<tr>
<th>Blue Dye</th>
<th>Radiopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene blue</td>
<td>Tc-99m Dextran</td>
</tr>
<tr>
<td>Isosulfan blue</td>
<td>Tc-99m HSA</td>
</tr>
<tr>
<td>Patent blue-V</td>
<td>Tc-99m Antimony sulfide</td>
</tr>
<tr>
<td>Cyalume</td>
<td>Tc-99m Nanocolloid</td>
</tr>
<tr>
<td>Flourescein</td>
<td>Au-198 colloid</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Sulfur colloid</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Stannous fluoride</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Stannous phytate</td>
</tr>
<tr>
<td></td>
<td>Tc-99m Microcolloidal albumin</td>
</tr>
</tbody>
</table>
Blue Dye

Methylene blue: diffuses to periphery
Cyalume: needs dark medium
Flourescein: fast diffusion to periphery

Patent blue-V: diffuse less to peripheral tissue
Isosulfan blue
Blue Dye

- 15-20 min before incision
- Isosulphan Blue %1, 2-5 ml
- Intradermal injection
- Massage gently
5-25nm: pass freely intercellular gaps
50-75nm: pinocytosis
75nm↑: stays at injection site
Radiocolloids for SLN Detection

Particle diameter:

- **3-15 nm**: Tc-99m-Nanocolloid (Rhenium sulfide colloid)
- **80 nm**: Tc-99m-Nanocolloid (albumin colloid)
- **40-1000 nm**: Tc-99m-sulfur colloid
- **400-5000 nm**: Tc-99m-tin colloid
Intradermal Injection:

Rich in lymphatics

superficial lesions
Subcutaneous injection

- subcutaneously 0.5cc
- Success rate 95% (colloid)
- 82% (blue dye)

Peritumoral Injection

- Peritumorally from different quadrants if possible
- 0.5cm distance
- 0.5ml
- Slow lymphatic flow
- SLN visualised relatively late
- 30% extra-axillary LN
- Deeper-located lesions

Subareolar-Periareolar Injection

Subareolar plexus drains breast lymphatics

Multifocal/multicentric tumors

• Painful
• Internal mammarian drainage?
Radiocolloid Injection-SLN Detection

- $^{99mTc}$-nanocolloid (Rhenium sulfur colloid)
- $^{99mTc}$-tin colloid
- 0.1-0.2 ml, ppd.
- Intradermal
- Massage
Comparison of blue dye and gamma probe guided sentinel lymph node biopsy techniques in breast cancer patients

ÖMER UGUR¹, M. FANI BOZKURT¹, ISKENDER SAYEK², GÖKHAN GEDIKOGLU³, ATAÇ BAYKAL², ERHAN HAMALOGLU², ILKER ETIKAN⁴, ALI KONAN², BELKIS ERBAS¹

Departments of ¹Nuclear Medicine, ²Surgery, ³Pathology and ⁴Biostatistics, Hacettepe University Faculty of Medicine, Ankara-Turkey

Table 2
Comparison of the gamma probe and blue dye for the localization of the SLN*

<table>
<thead>
<tr>
<th></th>
<th>Blue Dye</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Gamma Probe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>17 (60.7%)</td>
<td>11 (39.3%)</td>
<td>28 (100%)</td>
</tr>
</tbody>
</table>

* Gamma probe identified more SLN compared to blue dye and this is statistically significant
(Fisher’s exact chi-square test $p=0.03$)
Nanocolloid

Injection site

SLN

1. hour

Tin colloid

1. hour
SPECT/CT in SLN-Breast ca

Courtesy of Prof Giuliano Mariani
Breast Cancer

Courtesy of Prof Giuliano Mariani
Breast Cancer

Courtesy of Prof Giuliano Mariani
Added Value of SPECT/CT

• **Attenuation correction**
  – Better visualisation of non-visualised / barely visible LNs on planar imaging
  – Better imaging in obese patients

• **Identification of exact topographic localization** of SLNs

• **Identification of exact number, size and depth** of LNs
Gamma Probe
Blue & radioactive lymph node
Întratumoral Injection

• No lymphatics within tumor
• Risk of tumor seeding
• High interstitial and intracellular pressure
• Nieweg et al.* 97% success

ROLL (Radioguided Occult lesion localization)

ROLL

• To identify «difficult-to-locate» neoplastic lesions to be excised
• Direct image-guided intrallesional delivery of tracers that remains at the site of injection
• Tc99m-MAA (macroaggregated Albumin)
• Systemic administration of suitable tumor-seeking agents (Tc99m-MIBI, F-18 FDG...)

Mariani G et al, Radioguided Surgery Springer 2008
Zaknun JJ et al, EJNMMI, 2012
ROLL-Injection Technique

Mammography-guided

Ultrasonography-guided
Lesion Detection by US-ROLL

Courtesy of Prof Seyfettin ILGAN, Ankara
Insertion of needle-ROLL

Courtesy of Prof Seyfettin ILGAN, Ankara
Injection of Tc99m-MAA-ROLL

Courtesy of Prof Seyfettin ILGAN, Ankara
ROLL-Scintigraphy
SPECT/CT Imaging
ROLL-Pre/Intraoperative Gamma Probe
Lesion excision
Post-excision Gamma Probe
ROLL-Scintigraphy of Specimen

- Injection site
- Excised lesion margin
Case 1

Displacement of the guide-wire
Case 2

Added value of SPECT/CT
Case 3

Thick-walled cystic lesion
Case 4

Mammography-guided ROLL, lobular ca in situ
• «….Can we detect all sentinel nodes by conventional way (blue dye + scintigraphy + gamma probe) ??...»

• .......No (Unfortunately).
GOSST in Breast Ca

“SLNs may act like GHOSTs...”
• ~7% SLNs cannot be detected with routine scintigraphy & gamma probe ("ghost nodes")

• Undetected nodal spread and inadequate adjuvant treatment may account for a significant number of breast cancer-related deaths.

Kim et al, Cancer 2006;106:4–16
Wendler et al, EJNMMI 2010;37:1452-61
Tools for detecting SLNs - planar

- **Single D gamma probe**
  - handheld device
  - acoustic feedback
  - No sense of depth
  - Intraoperative

- **2D scintigraphy**
  - projective 2D image
  - stationary device
  - No sense of real depth
  - Preoperative

**2D portable scintigraphy**
- handheld device
- projective 2D image
- No sense of real depth
- intraoperative

*Modified from SurgicEye presentation*
Tools for detecting SLNs – 3D

- **3D SPECT/CT, PET/CT**
  - anatomical and functional
  - stationary device
  - preoperative

- **3D freehand SPECT**
  - depth information
  - anatomical and functional
  - visual and acoustic feedback
  - integration of preoperative nuclear medicine data intraoperatively
  - Ability to NAVIGATE

Modified from SurgicEye presentation
Friendly Ghost...

GOSTT

(radio)Guided
IntraOperative
GOSTScintigraphic
Tumor
GOSTTargeting
Intraoperative Scintigraphy
Hand-held Cameras / Navigators

Sentinella

declipseSPECT
- handheld-Gammasonde
- dreidimensionale Lokalisierung im Raum durch Landmarker
- Bildakquisition durch „Scanner“ über 1 – 3 min.
- dreidimensionale Rekonstruktion und Überlagerung mit Op-Situs

CrystalCam
Gamma camera system for nuclear medical imaging
The GOSTT concept and hybrid mixed/virtual/augmented reality environment radioguided surgery

R. A. Valdés Olmos 1, 2, S. Vidal-Sicart 3, F. Giannmarile 4
J. J. Zaksun 5, F. W. B. Van Leeuwen 2, G. Mariani 6

Figure 3.—Schematic visualization of mixed reality in the operating room. In the upper row, after loading SPECT/CT into the navigation system, images are incorporated to the laparoscopy procedure in order to create a hybrid reality environment, which is displayed on screen to support the “see and navigate” approach toward iliac sentinel lymph nodes (SLNs). In the lower row SPECT/CT is already displayed into the field of view of the surgeon, who uses special spotlights to localize SLNs in the head and neck. The approach of “see, operate, and see again” of the surgeon is then complemented by real-time navigation. Note the reference target (0v/D) on the left frontal area of the patient’s skull. This SRT will enable the navigation system to virtually extrapolate 3D SPECT/CT information to the position of the patient in the operating room.
The GOSTT concept and hybrid mixed/virtual/augmented reality environment radioguided surgery

R. A. VALDÉS OLMO 1, 2, S. VIDAL-SICART 3, E. GIAMMARILE 4 J. J. ZAKNUN 5, F. W. B. VAN LEEUWEN 2, G. MARIANI 6

<p>| TABLE 1.—Some existing PIT devices (commercially available or prototypes). |</p>
<table>
<thead>
<tr>
<th>Internet site for additional information</th>
<th>Original city and country</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTABLE GAMMA CAMERAS</td>
<td></td>
</tr>
<tr>
<td>eZ-Scope</td>
<td><a href="http://www.anzai-med.co.jp">www.anzai-med.co.jp</a></td>
</tr>
<tr>
<td>Minicam II</td>
<td><a href="http://www.eminstruments.com">www.eminstruments.com</a></td>
</tr>
<tr>
<td>Sentinella</td>
<td><a href="http://www.oncovision.es">www.oncovision.es</a></td>
</tr>
<tr>
<td>IP Guardian II</td>
<td><a href="http://www.li-tech.it">www.li-tech.it</a></td>
</tr>
<tr>
<td>CrystalCAM</td>
<td><a href="http://www.crystal-photonics.com">www.crystal-photonics.com</a></td>
</tr>
<tr>
<td>MediPROBE</td>
<td><a href="http://www.na.infn.it">www.na.infn.it</a></td>
</tr>
<tr>
<td>Intraoperative gamma camera GE</td>
<td>prototype</td>
</tr>
<tr>
<td>Marginator (beta camera)</td>
<td><a href="http://www.intra-medical.com">www.intra-medical.com</a></td>
</tr>
<tr>
<td>NEAR-INFRARED FLUORESCENCE CAMERAS</td>
<td></td>
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<tr>
<td>HyperEye</td>
<td><a href="http://www.mizuhomedical.co.jp">www.mizuhomedical.co.jp</a></td>
</tr>
<tr>
<td>SPY imaging system</td>
<td><a href="http://www.novadaq.com">www.novadaq.com</a></td>
</tr>
<tr>
<td>Pinpoint (laparoscopic)</td>
<td><a href="http://www.novadaq.com">www.novadaq.com</a></td>
</tr>
<tr>
<td>PDE (Photodynamic Eye)</td>
<td><a href="http://www.hamamatsu.com">www.hamamatsu.com</a></td>
</tr>
<tr>
<td>FLARE/mini-FLARE</td>
<td><a href="http://www.centerformolecularimaging.com">www.centerformolecularimaging.com</a></td>
</tr>
<tr>
<td>Image HUB IHD + D-light P System (laparoscopic)</td>
<td><a href="http://www.karlstorz.com">www.karlstorz.com</a></td>
</tr>
<tr>
<td>3D IMAGE GENERATION DEVICES</td>
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<tr>
<td>Decipse</td>
<td><a href="http://www.surgiceye.com">www.surgiceye.com</a></td>
</tr>
<tr>
<td>HYBRID OPTICAL/GAMMA DEVICES</td>
<td></td>
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<tr>
<td>Hybrid Mini Gamma camera</td>
<td>prototype</td>
</tr>
<tr>
<td>Hybrid Sentinella</td>
<td><a href="http://www.oncovision.es">www.oncovision.es</a></td>
</tr>
<tr>
<td>Opto-nuclear probe (no imaging)</td>
<td><a href="http://www.eurorad.com">www.eurorad.com</a></td>
</tr>
</tbody>
</table>
Intraoperative Imaging & Navigation

- **depth** information
- visual and acoustic feedback
- **intraoperative**
  - before intervention for **guidance**
  - after intervention for **quality control**
Radio-guided surgery

R. A. Valdés Olmos, S. Vidal-Sicart und O. E. Nieweg; Technological innovation in the sentinel node procedure: towards 3-D intraoperative imaging; Eur J Nucl Med Mol Imaging,
All information in the OR, 3D and in-situ

3D imaging, visualization and image guided tumor surgery with declipse®SPECT

Images courtesy of Prof. Taffurelli (Gynecology) and Prof. Fanti, Dr. Santi and Dr. Fantini (Nuclear Medicine) at Policlinico S. Orsola Malpighi, Bologna, Italy
Imaging & Navigation

Set up  \hspace{1cm} Scan  \hspace{1cm} Visualize\(^1\)  \hspace{1cm} Navigate

Modified from SURGICeye
They offer an in-situ localization, visualization and margin control in real-time and 3D for non-palpable lesions.

They help to achieve a low rate of positive margins (R1 margins) results in reduced reoperation rates.

1Ramesh HSJ et al., Recurrence after ROLL lumpectomy for invasive breast cancer, The Breast (2008), doi:10.1016/j.breast.2008.05.005
3D ROLL/RSL: Case

Minimally invasive but complete resection of radioactively marked tumor

Images courtesy of Dr. Oscar R. Brouwer and Dr. Jose van der Hage, NKI, Amsterdam, THE NETHERLANDS.
Visualization of lesion and SLNs in **ROLL + SLNB (SNOLL)** technique

Images courtesy of Prof. Taffurelli (Gynecology) and Prof. Fanti, Dr. Santi and Dr. Fantini (Nuclear Medicine) at Policlinico S. Orsola Malpighi, Bologna, Italy.
## Evolution of axilla treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Initiator</th>
<th>Procedure</th>
<th>Morbidity</th>
<th>Current FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1894</td>
<td>Halsted</td>
<td>Axillary Lymph Node Dissection</td>
<td>High</td>
<td>0%</td>
</tr>
<tr>
<td>1993</td>
<td>Krag / Alex</td>
<td>SLNB with Tc99m</td>
<td>Low</td>
<td>8.8%</td>
</tr>
<tr>
<td>1994</td>
<td>Giuliano</td>
<td>SLNB with blue</td>
<td>Medium</td>
<td>10.9%</td>
</tr>
<tr>
<td>1998</td>
<td>Cox</td>
<td>SLNB with blue and Tc99m</td>
<td>Low</td>
<td>7.0%</td>
</tr>
<tr>
<td>2002</td>
<td>Schillaci / Scopinaro</td>
<td>SLNB with portable gamma camera</td>
<td>Low</td>
<td>?</td>
</tr>
<tr>
<td>2009</td>
<td>Troyan</td>
<td>SLNB with ICG</td>
<td>Low</td>
<td>?</td>
</tr>
<tr>
<td>2010</td>
<td>Schnelzer / Paepke</td>
<td>SLNB with declipse®SPECT</td>
<td>Minimal</td>
<td>?</td>
</tr>
</tbody>
</table>

Alternative Approaches...

• İntraoperative scintigraphy + USG
  – To differ sentinel lymph nodes from non-sentinel LNs
  – To facilitate image-guided biopsy
Clinical Workflow

- Scintigraphic Imaging
- DICOM Export/Import
- Automatic Registration
- Fused Visualization

Modified from SURGICeye
Current SLNB and non-surgical SLNB

Mapping SLNs precisely in ultrasound and taking biopses with sufficient tissue can avoid the surgical removal of SLNs.

declipse®SPECT
Ultrasound enables clear separation between non-SLNs and SLNs and guide placement of biopsy needle in correct SLN.
Clinical Application SPECT/US - SLNB

$^{99m}$TcO$_4$-Colloid  freehandSPECT / US real-time fusion
(GE Logiq E9, VNav® / decliseSPECT® Surgiceye)
Sentinel lymph node

- sonogram
- navigated Fusion
- freehand SPECT

left inguinal – transversal section

Martin Freesmeyer

Jena 30.10.2012

Modified from SURGICEYE
Advantages

- 3D hand-held SPECT images finds hidden structures not visible in 2D scintigraphy
- Fusion of anatomical and functional images enables easier diagnostics and biopsy guidance
- Optimized workflow – complete examination including biopsy in one session in less than 15min

Differentiation of sentinel vs. non-sentinel lymph node in breast cancer patient.

Modified from SURGICeye
Alternative Approaches: Hybrid Tracers

Sensitivity:
- E-15 mol
- E-12 mol
- E-9 mol
- E-6 mol
- E-3 mol

Resolution:
- E-3mm
- E-2 mm
- E-1 mm
- 1 mm
- E+1 mm

Chin et al., EJNMMI 2013
Hybrid Tracers

Radioactive + Fluorescent stable complexes

Image courtesy of Dr. Fijs W. B. van Leeuwen, Radiology Department, LUMC, Leiden, THE NETHERLANDS
Using a hybrid tracer, the surgeon can find the gross area (>5mm, picture a/d) using the radioactive emission and then use the fluorescent component for minimal resection (<5mm, pictures c/f).

Methodology

- Depth information and gross navigation based on freehand SPECT
- Fine navigation based on fluorescence
Hybrid Technology

Fluorescent radiocolloids: are hybrid tracers the future for lymphatic mapping?

Sergi Vidal-Sicart1 · Fijs W. B. van Leeuwen2 · Nynke S. van den Berg2 · Renato A. Valdés Olmos2,3

Evaluation of a radioactive and fluorescent hybrid tracer for sentinel lymph node biopsy in head and neck malignancies: prospective randomized clinical trial to compare ICG-99mTc-nanocolloid hybrid tracer versus 99mTc-nanocolloid

Ingo Stoffels1,2,3 · Julia Leyh1,2,3 · Thorsten Pöppel4 · Dirk Schadendorf1,2,3 · Joachim Klode1,2,3

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iROLL: does 3-D radioguided occult lesion localization improve surgical management in early-stage breast cancer?

Christina Bluemel¹ · Andreas Cramer² · Christoph Grossmann² · Georg W. Kajdi¹ · Uwe Malzahn³ · Nora Lamp⁴ · Heinz-Jakob Langen⁵ · Jan Schmid¹ · Andreas K. Buck¹ · Hanns-Jörg Grimminger² · Ken Herrmann¹

<table>
<thead>
<tr>
<th>day before surgery</th>
<th>day of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoscintigraphy</td>
<td></td>
</tr>
<tr>
<td>1) Ultrasound-guided intratumoral injection</td>
<td></td>
</tr>
<tr>
<td>2) Planar images</td>
<td></td>
</tr>
<tr>
<td>3) Periareolar injection</td>
<td></td>
</tr>
<tr>
<td>4) Early and late planar images with or without SPECT/CT</td>
<td></td>
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<tr>
<td>ultrasound-guided hook wire insertion</td>
<td></td>
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<tr>
<td>iROLL</td>
<td></td>
</tr>
<tr>
<td>1) SLNB</td>
<td></td>
</tr>
<tr>
<td>2) Preincision breast scan</td>
<td></td>
</tr>
<tr>
<td>3) Breast lesion excision</td>
<td></td>
</tr>
<tr>
<td>4) Postexcision breast scan and specimen scan including measurement</td>
<td></td>
</tr>
<tr>
<td>5) Additional resection if necessary</td>
<td></td>
</tr>
<tr>
<td>histopathology</td>
<td></td>
</tr>
</tbody>
</table>

![Image of surgical procedure and equipment]
iROLL: does 3-D radioguided occult lesion localization improve surgical management in early-stage breast cancer?

Christina Bluemel¹ · Andreas Cramer² · Christoph Grossmann² · Georg W. Kajdi¹ · Uwe Malzahn³ · Nora Lamp⁴ · Heinz-Jakob Langen⁵ · Jan Schmid¹ · Andreas K. Buck¹ · Hanns-Jörg Grimminger² · Ken Herrmann¹

Conclusion iROLL is a well-tolerated and feasible technique for localizing early-stage breast cancer in the course of breast-conserving surgery, and is a suitable replacement for WGL. As a single image-based procedure for localization of breast lesions and sentinel nodes, iROLL may improve the entire surgical procedure. However, no advantages of the image-guided procedure were found with regard to prediction of complete tumour resection.
New Horizons

• Intraoperative PET Navigation Systems

• Robotic Radioguided Surgery
In order to guarantee repetability and increase image quality letting the scan of declipse®SPECT be automatized is valid approach.