Precision medicine has evolved from invasive surgery in the past..

“There is no more science to surgery that to butchering.”

Edward Thurlow 1811
..to a highly refined technical endeavor.
New technologies make surgery accessible..
.. But pinpointing targets for surgeons to resect remains a challenge

van der Poel et al., *Eur Urol 2011*, Buckle et al., *J Nucl Med 2012*
Interventional molecular imaging – a multidisciplinary approach
Imaging technologies can help differentiate between benign and malignant tissue...
...by illumination specific features
Like any intervention it is essential to pick the right tools for the job.
Interventional molecular imaging: Radioguided surgery vs. Fluorescence guided surgery

Radioguided surgery

Accumulation SN
e.g. $^{99m}$Tc-Nanocolloid

Receptor targeting
e.g. $^{99m}$Tc-PSMA and $^{111}$In-DOTATOC

Lymphatic mapping
e.g. Fluorescein, Methylene Blue and ICG

Metabolism
e.g. 5-Aminolevulinic Acid

Angiography
e.g. Fluorescein and ICG

Clearance
(e.g. Fluorescein (renal) and ICG (hepatobiliary))

Van Leeuwen et al. JNM 2020
Penetration depth: Radioactive vs. Fluorescence signals

Radioguided surgery

Absorption/Scattering

Resolution

> 10 cm

Fluorescence guided surgery

Absorption/Scattering

Resolution

< 1 cm

Van Oosterom et al., EJNMMI Research 2014

Penetration depth: Radioactive vs. Fluorescence signals

Graph showing penetration depth and normalised signal for SPECT, Fluorescence U-SPECT-BioFluo, and Fluorescence IVIS.
Hybrid approaches that combine radio- and fluorescence guidance help address the full surgical complexity
Molecular imaging starts with tracer development
Lymphatic imaging: chemical properties dictate physiology and molecular uptake

(+): SN specificity
(+): Long retention (> 30h after tracer administration)
(+): Preoperative imaging

(-): Rapid clearance (no specificity)
(+): Optical identification

vd Berg et al QJNMMI 2014
Hybrid tracers help combine the best of both worlds e.g. ICG-\(^{99m}\)Tc-nanocolloid

“standard” in Europe

van der Poel et al., *Eur Urol* 2011
The complementarity of the imaging signatures can be used to realize precision surgery

Meershoek et al. JNM 2019
The concept of using hybrid tracers in clinical trials is gaining traction

<table>
<thead>
<tr>
<th>Hybrid tracer</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG-$^{99m}$Tc-nanocolloid</td>
<td>&gt;1500</td>
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<tr>
<td>$^{131}$I-Fluorescein</td>
<td>&gt;20</td>
</tr>
<tr>
<td>$^{123}$/$^{125}$I-methylen blue</td>
<td>&gt;20</td>
</tr>
<tr>
<td>$^{111}$In-DOTA-gerentuximab-IRDye800CW</td>
<td>&gt;15</td>
</tr>
<tr>
<td>$^{68}$Ga-IRDye800CW-BNN</td>
<td>&gt;14</td>
</tr>
<tr>
<td>FITC-$^{125}$I-CEA mAb</td>
<td>&gt;5</td>
</tr>
<tr>
<td>$^{124}$I-cRGDY-PEG-C</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Cerenkov</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

Van Leeuwen et al. JNM 2020
Various preclinical developments are ongoing e.g. Cy5-\(^{99m}\)Tc-PSMA
Technologies - radioguided surgery
How can we translate imaging at nuclear medicine to the OR?
Open surgery: intraoperative use of radiation detecting modalities provides outcome

Gamma probe

Portable gamma camera

Tracking fiducials to support freehand SPECT imaging
Converting to laparoscopic surgery creates new challenges

Horn et al. Eur Urol 2019
DROP-IN gamma probe to facilitate lymphatic mapping procedures

$^{99m}$Tc-PSMA-I&T guided robotic surgery – same probe, different $^{99m}$Tc tracer

Round 2: Surgical guidance (different tracer)

Round 2: Surgical guidance (different tracer administration)

Step 1: Administration of $^{68}$Ga-PSMA-11
100 MBq

Step 2: RARP + ePLND

Step 3: Ex vivo evaluation

Collimatti et al. under revision
Technologies - fluorescence guided surgery

One eye-witness weighs more than ten hearsays — Seeing is believing all the world over.

(Plautus)
Real-time lesion identification in anatomical context
With hybrid tracers radio- and fluorescence guided surgery work together.
Multicolor imaging allows us to address the anatomical complexity.
This is made possible by using differently colored tracers for different targets.

Intraoperative differentiation between key features can help reduce surgical morbidity.
Identifying primary tumor margins while allowing with lymphatic mapping

Martijn et al. manuscript in preparation

Primary tumor margins
(EMI-137; Cy5)

SN
(ICG- 99mTc-nanocolloid)
‘GPS-like’ navigation
Navigating surgical tools in preoperative roadmaps, connecting the dots
Registering preoperative images to the patient
First clinical implementation studies promising, but intraoperative imaging remains imperative to confirm the target location.
Conclusion: integrating technologies helps advance image guided surgery.
Acknowledgements