Recurrent Differentiated Thyroid Cancer: towards Personalized Treatment based on Evaluation of Tumor Characteristics with PET

A. Bockisch, I. Binse
PET Imaging

in
Differentiated Thyroid Cancer (DTC)* and
Poorly Differentiated Thyroid Cancer (PDTC)*

(Radiopharmaceuticals)

* In the remainder of the presentation summarized under DTC
PET Imaging in DTC

PET is just a device to image the 3D distribution of positon emitters.

There is a large variety of such radiopharmaceuticals

a) unspecific like $[^{18}\text{F}]$FDG (sensitive to many cancers)

b) highly specific like $[^{124}\text{I}]$KI or $^{68}\text{Ga}$-DOTATOC

Radiopharmaceuticals may result in complementary information.

e.g.

$^{124}\text{I}$ is extremely sensitive to iodine avid mets of DTC

$[^{18}\text{F}]$ FDG is especially sensitive to iodine negative mets.
124I - PET(/CT) - imaging

131I - scintigraphy
4 GBq

124I – PET/CT; 25 MBq
thyroid remnant +
lymph node metastasis

45 y/o pt suffering from follicular thyroid cancer
pT3NxMx after thyroidectomy and prior to 1st radioiodine therapy
Thyroid tissue or Metastasis?

$^{124}$I - PET

PET/CT

PET/MRT
Thyroid Remnant or Metastasis?

CT

MRT
$^{68}$Ga DOTATOC – PET(/CT)

$^{111}$In – SSTR – Scintigraphy

DOTATOC-PET
poorly differentiated DTC
iodine negative
initial diagnosis 15 years ago

(FDG is especially sensitive to iodine negative metastases of DTC.)

\( [^{18}\text{F}]-\text{FDG} - \text{PET} \)

\( (\text{SUV}_{\text{max}} = 42) \)
[\(^{124}\text{I}\)]iodide PET/CT
45 MBq, 24h p.a.

PET 1h p.i. 360 MBq [\(^{18}\text{F}\)]FDG

41 y/o pt. with bone metastases of follicular DTC prior to 1\(^{\text{st}}\) RIT
**124I PET/CT Imaging in Extended Disease**

important:

detecting intra lesion inhomogeneity

→ cross sectional imaging with high spatial resolution needed

→ anatomic coregistration with CT or MRI at least very helpful
Radioiodine Therapy and $^{124}$I Dosimetry in DTC and PDTC
DTC: Rate of Recurrences with/without $^{131}$I-therapy

Mazzaferri et al. 1990
RIT in Differentiated Thyroid Cancer (DTC)

- first reports > 70 years ago, well etabliert since 50 years
- high therapeutic width
- very low rate of side effects
- successful

→ empiric activities

- concept A
  fixed therapeutic activities
  (activity might depend on risk)

- concept B
  therapy activity chosen
  based on tolerable activity
  of organ at risk (bone marrow)

Improvement?

- concept C
  therapeutic activity based on lesion dosimetry
  and considering tolerable activity of organ at risk
Dosimetry in DTC

**Why?**

1. results in individually determined therapeutic activity
   a) avoids fatal side effects (which are very rare)
   b) avoids under treatment
   c) avoids useless treatment,
      (when effective activity is out of reach)

2. allows modification of radioiodine therapeutic concept
   a) redifferentiation
   b) Li\(^+\) – premedication
   c) thyroid blocking with high (stable) iodine doses
   d) rTSH \(\leftrightarrow\) endogenous TSH stimulation

3. may lead to multimodale therapy

4. gives quantitative determination of dose response
Prerequisite for Dosimetry

- absolute quantification
  specific tracer and/or images without superposition
  + sharp images
  + absorption and scatter correction
- volume
- kinetics (various measurement time points)
- knowledge about activity distribution
  *The range of the radiation and inverse square law.*

Neither iodine kinetics nor biologic response of the therapy must be altered by the imaging or the dosimetric radiotracer.
## RIT of DTC – Organs at Risk

<table>
<thead>
<tr>
<th>organ at risk</th>
<th>(surrogate) toxicity parameter</th>
<th>intended „limits“</th>
</tr>
</thead>
<tbody>
<tr>
<td>bone marrow</td>
<td>blood dose</td>
<td>2.0 Gy</td>
</tr>
<tr>
<td>lungs</td>
<td>whole body retention activity at 48 h</td>
<td>4.4 GBq</td>
</tr>
<tr>
<td></td>
<td>without lung metastases</td>
<td>3.0 GBq</td>
</tr>
<tr>
<td></td>
<td>with lung metastases</td>
<td></td>
</tr>
</tbody>
</table>

**131I-PET Dosimetry: The Essen Protocol**

### lesion-dosimetry

- **131I lesion dose/activity [Gy/GBq] (LDpA)**

### blood dose as surrogate for bone marrow dose

- **dose $D_\beta$ + dose $D_\gamma$$^{131I}$ - activity resulting in the blood dose of (2 Gy).

- **131I – therapy activity**
## Dosimetry, Example

Bone metastases of follicular thyroid cancer

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBA (GBq)</strong></td>
<td><strong>LDpA (Gy/GBq)</strong></td>
</tr>
<tr>
<td>6</td>
<td>10 – 350</td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

**RIT:** \( A_{appl} = 10 \text{ GBq} \Rightarrow Dose \approx 100 – 3500 \text{ Gy} 

LDpA: lesion dose per activity  
CBA: activity that results in 2 Gy bone marrow dose  
CBA: activity that results in „accepted“ whole body activity retention at 48 h  
C_{PET}: activity concentration measured in PET

### Side effects (expected, as \( A_{appl} \approx 2 \cdot \text{CBA} \)):

- lymphocytes \( \downarrow \) as far as 0.2 /nl \((n = 1.2 – 3.4 / \text{nl})\)
- fever at day 6 (\( \rightarrow \) antibiotics)
- bone pain (opiates)
Individualized Therapy after $^{124}$I - Dosimetry

Radioiodine therapy using 10 GBq $^{131}$I extensive bone metastases
4 Gy bone marrow- $^{124}$I - PET / CT

dose at 10 GBq

prior to 1st radioiodine therapy

4 months later
Which $^{131}$I - Radiation Dose is Needed?

- „sufficient differentiation given, tumor doses up to 800 Gy (and even higher) may be reached“
- „typical dose for thyroid remnant ablation: 300 Gy“
- „typical ablation dose for metastases > 80 Gy“
- „for doses < 35 Gy → cure is very unlikely“

These statements are quite good indications not completely in agreement to our experience.

→ Dose response data with state of the art dosimetry need to be generated – taking tumor biology and heterogeniety of metastases into consideration.
**Achievable Lesion Dose**

Own data of 207 pts with DTC pT4 or known metastases

<table>
<thead>
<tr>
<th></th>
<th>not measurable ( \rightarrow ) volume &lt; 0.51 ml</th>
<th>volume derived from PET and/or CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDpA (Gy/GBq) *</td>
<td>LDpA (Gy/GBq) *</td>
</tr>
<tr>
<td>thyroid remnant</td>
<td>&gt; 118 (1 - 3628)</td>
<td>421 (22 - 2625)</td>
</tr>
<tr>
<td>„lymph node metastases“</td>
<td>&gt; 7 (1 - 347)</td>
<td>7 (1 - 233)</td>
</tr>
<tr>
<td>lung metastases</td>
<td>&gt; 23 (1 - 208)</td>
<td>7 (1 - 29)</td>
</tr>
<tr>
<td>bone metastases</td>
<td>&gt; 15 (2 - 161)</td>
<td>20 (1 - 334)</td>
</tr>
</tbody>
</table>

* median (minimum – maximum)

large variation of doses in the metastases between (0) 1 and 350 Gy/GBq
### Statistics for Applying Standard Activities

Using dose/activity distribution from 207 pts with DTC pT4 and metastases of known volume (own data)

<table>
<thead>
<tr>
<th>activity (GBq)</th>
<th>thyroid remnant ((n=66))</th>
<th>lymph node metastases ((n=35))</th>
<th>lung metastases ((n=10))</th>
<th>bone marrow ((n=26))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>likelyhood for 300 Gy</td>
<td>likelyhood to reach 80 Gy lesion dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>62%</td>
<td>9%</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>3.7</td>
<td>84%</td>
<td>29%</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>7.4</td>
<td>91%</td>
<td>46%</td>
<td>30%</td>
<td>64%</td>
</tr>
<tr>
<td>11</td>
<td>97%</td>
<td>51%</td>
<td>50%</td>
<td>69%</td>
</tr>
<tr>
<td>15</td>
<td>100%</td>
<td>60%</td>
<td>60%</td>
<td>73%</td>
</tr>
<tr>
<td>18.5</td>
<td>100%</td>
<td>60%</td>
<td>60%</td>
<td>77%</td>
</tr>
</tbody>
</table>

(Only) app. 30 - 60% of all metastases get doses of 80 Gy or more at 7.4 GBq – the (curing) minimal response limit according to Maxon

Keep in mind: reaching the dose is not equivalent to cure!
Statistics for Applying Standard Activities

„Toxicity limits“: Blood dose > 2 Gy and/or whole body activity retention at 48 h > 4.4 GBq (> 3.0 in case of lung mets)

<table>
<thead>
<tr>
<th>Activity (GBq)</th>
<th>bone marrow*</th>
<th>lungs*</th>
<th>bone marrow ∩ lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>likelihood to exceed limits</td>
<td>to exceed both limits</td>
<td></td>
</tr>
<tr>
<td>3.7</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>0</td>
</tr>
<tr>
<td>7.4</td>
<td>3 (2 %)</td>
<td>5 (3 %)</td>
<td>0</td>
</tr>
<tr>
<td>11.1</td>
<td>8 (5 %)</td>
<td>11 (7 %)</td>
<td>0</td>
</tr>
<tr>
<td>14.8</td>
<td>18 (11 %)</td>
<td>28 (17 %)</td>
<td>2 (1 %)</td>
</tr>
<tr>
<td>18.5</td>
<td>39 (24 %)</td>
<td>42 (25 %)</td>
<td>7 (4 %)</td>
</tr>
</tbody>
</table>

Using dose/activity distribution from of 162 pts (own data)

Application of 7.4 GBq has a small risk (5 %) for exceeding „toxicity limits“ * however: of macroscopic mets 40% of lymph node mets, 40 % of lung mets and 30 % of bone mets would not reach a lesion dose of 80 Gy even when using 15 GBq.

* Tuttle et al. (J. Nucl. Med. 2006; 47: 1587)
8 % of 535 pts with DTC showed corresponding side effects
### Statistics of Applicable Activities, when Avoiding Side Effects

**Own data, 162 pts with DTC**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>average</td>
<td>0.094</td>
<td>25</td>
<td>average</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>SD</td>
<td>0.046</td>
<td>9</td>
<td>SD</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Median</td>
<td>0.083</td>
<td>25</td>
<td>Median</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.030</td>
<td>5</td>
<td>Minimum</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.362</td>
<td>68</td>
<td>Maximum</td>
<td>59</td>
<td>440</td>
</tr>
</tbody>
</table>

Applicable activity that results in a blood dose of 2 Gy or a whole body retention activity at 48 h of 4.4 GBq respectively, which are considered to be „safe“. 
Iodine Positive Metastases of DTC

Individualized therapy

1.) high dose achievable
   → RIT

2.) low dose expected
   → measures to increase the dose
      increased activity
      e.g. Li⁺, redifferentiation

3.) mixed metastases
   → RIT + other treatment

Severe side affects can be avoided.
Endogeneous ↔ Exogeneous
TSH stimulation

rhTSH
1.5 Gy/GBq

THW
15 Gy/GBq

Images made at the MHH
**Endogenous ↔ Exogenous Stimulation**

LDpA = lesion absorbed dose in Gy pro GBq applied $^{131}$I activity

<table>
<thead>
<tr>
<th></th>
<th>rhTSH group</th>
<th>THW group</th>
<th>Difference in means</th>
<th>95%-confidence interval</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated means from the mixed model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDpA</td>
<td>29.398</td>
<td>52.93</td>
<td>-22.495</td>
<td>-51.052; 6.062</td>
<td>0.1208</td>
</tr>
</tbody>
</table>

Please note: This was not a randomized prospective study

Freudenberg et al.
Redifferentiation:
Changing the thyroid cell characteristics such, that iodine uptake is reestablished or increased.

Various medications:

1.) retinoids (vitamine A)  
   poor success

2.) glitazones (e.g. Rosiglitazone)  
   some success

3.) kinase inhibitors  
   promising

Redifferentiation might have other positive effects.
Iso Retinoid Redifferentiation Therapy

23 y/o female, papillary thyroid cancer, T3N1M1 (pulmo)

Prior to retinoid therapy

After 7 months with 40 mg iso retinoids

Some effect, but not therapeutically helpful
Redifferentiation using Rosiglitazone

60 y/o female with follicular TC, ED 15 years ago, pT4N0M1 (os) 5 years before radioiodine therapy with a total of 32 GBq, now progression

\[ ^{18}F\text{FDG PET } \text{SUV}_{\text{max}} = 3.2 \quad ^{124}\text{I PET } \text{SUV}_{\text{max}} = 4.3 \]

prior to
6 month of redifferentiation therapy

\[ ^{18}F\text{FDG PET } \text{SUV}_{\text{max}} = 1.1 \quad ^{124}\text{I PET } \text{SUV}_{\text{max}} = 41.9 \]

after

Good success, following RIT \( \rightarrow \) two years stable disease.
Oncocytic DTC, Initial Diagnosis 16 years ago

\[^{124}\text{I}]\text{KI}\]

\[^{68}\text{Ga-DOTATOC}\]

\[^{18}\text{F}]\text{FDG}\]
Indications

1.) prior to first radioiodine therapy in high risk DTC
   a) T4 stage
   b) known or suspected metastases

2.) in recurrence or persisting tumor

3.) prior to intended high activity therapy (e.g. > 10 GBq)

4.) prior to assumingly non curing radioiodine therapy
    before redifferentiation therapy
    for iodine kinetics modulation, e.g. TSH stimulation, Li+ planning of multimodal therapy
50 y/o male pt. follicular partly insular TC, bone metastases Primary diagnosis and surgery 12/04 initial $^{124}$I-dosimetry → high radiation dose by RIT achievable however spinal cord is under risk!
"Modified" Radioiodine therapy

→ implantation of a silicone absorber between spinal cord and tumor

followed by directed radioiodine therapy
I PET/CT Imaging

11/05 compression of spinal cord from fast growing tumor relapse L2

→ neoadjuvant radiotherapy (40 Gy) 12/05-01/06

tumor resection (R2) and intraoperative boost radiotherapy (20 Gy) 2/06
Molecular Targeted Therapies

off-label use of different cancer therapies since 1/08

**[18F]FDG - PET**

1/08 3/08 5/08 9/08 11/08 1/09 6/09 7/09

- Sorafenib 2/08-9/09
- Sunitinib 11-12/08
- Thalidomide + Dacarbazine 12/08-1/09
- Aurora B Kinase Inhibitor until 12/10

- patient enjoyed cycling until 10/2009 (12-15.000 km/y)
- fixateur interne broke 11/10, paraparesis, surgical stabilisation 12/10
- exitus 6/11

Combination of various therapies directed by cutting edge imaging gave the patient > 5 years survival nearly 5 years in in good quality of life.