124 Iodine girentuximab (CAIX) PET/CT: new perspectives for the management of renal masses

The view of the urologist

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Epidemiological trends in RCC

- Renal Cell Carcinoma (RCC) accounts for 3% of all solid tumors.
- During the 20 past years worldwide incidence has increased by 2.70% /y in men and by 3.74% in females.
- About 30,000 patients /y diagnosed with kidney cancer within the EU; approximately 15,000 deaths of the disease.

Remontet et al.: INSERM, FRANCIM, IVS., 2003
The Incidence of all Tumor Stages is Increasing

Hock, J Urol 2002

The incidence of organ confined tumors is increasing more rapidly
A continuous trend towards earlier detected tumors and increased rates of mini-invasive surgery (1050 patients – 1984/2007, Rennes)
2009 TNM Classification

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour

T1 Tumour ≤ 7 cm in greatest dimension, limited to the kidney
   T1a Tumour ≤ 4 cm in greatest dimension, limited to the kidney
   T1b Tumour > 4 cm but ≤ 7 cm in greatest dimension

T2 Tumour > 7 cm in greatest dimension, limited to the kidney
   T2a Tumour > 7 cm but ≤ 10 cm in greatest dimension
   T2b Tumours > 10 cm limited to the kidney

T3 Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
   T3a Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia
   T3b Tumour grossly extends into the vena cava below the diaphragm
   T3c Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava

T4 Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Renal tumors: Clinical presentation in 2010

- Incidental tumors
  - 60-70% vs 10% in the 70s
  - Of lower stages and lower grades than their symptomatic counterpart

- Hematuria, flank pain, palpable mass (10-20%)

- Systemic symptoms (asthenia, anorexia, weight loss, cough, bone pain, (5-10%)

Patard et Al., BJU Int 2002
Diagnosis=Imaging

- Abdominal CT is the standard imaging technique
  - With contrast injection (4 phases)
  - Contrast enhancement measurement++
  - With thoracic imaging for M Staging
- MRI
  - ESRD, Cystic tumors, IVC invasion staging
- FDG-PET: Optional
  - No place for diagnosis
  - Limited place in the metastatic setting
- Bone scan, Brain CT: in case of symptoms

EUA guidelines 2007
Ultrasound Imaging

- A lot of incidental tumors are discovered by US
- Distincts solid from liquid masses
- allows: tumor measurement, location, echogenicity
- Malignant tumors are typically iso-echogenic masses
- Contrast Enhanced US looks promising (diagnosis?; early response assessment following TKI treatment)
Typical SRM with significant contrast enhancement
Tumor biopsy

- Is gaining an increasing role
  - Proven reliability and safety
  - Before ablative treatments or active surveillance protocols
  - Systematic tumor biopsy for SRM (<4 cm) in patients suitable for surgery is still controversial

- Obvious indications
  - Suspicion of renal metastases or lymphoma
  - Non resectable tumor before targeted therapy
  - High risk patients

EAU Guidelines 2010
### Solid Renal Tumors: An Analysis of Pathological Features Related to Tumor Size

Igor Frank, Michael L. Blute, John C. Cheville, Christine M. Lohse, Amy L. Weaver and Horst Zincke

From the Departments of Urology (IF, MLB, HZ), Pathology (JCC), and Health Sciences Research (CML, ALW), Mayo Medical School and Mayo Clinic, Rochester, Minnesota

#### Tumor Size (cm) vs. No. Benign (%) vs. No. RCC (%)

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>No. Benign (%)</th>
<th>No. RCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–Less than 1.0</td>
<td>37 (46.3)</td>
<td>43 (53.8)</td>
</tr>
<tr>
<td>1.0–Less than 2.0</td>
<td>38 (22.4)</td>
<td>132 (77.7)</td>
</tr>
<tr>
<td>2.0–Less than 3.0</td>
<td>75 (22.0)</td>
<td>266 (78.0)</td>
</tr>
<tr>
<td>3.0–Less than 4.0</td>
<td>71 (19.9)</td>
<td>285 (80.1)</td>
</tr>
<tr>
<td>4.0–Less than 5.0</td>
<td>37 (9.9)</td>
<td>336 (90.1)</td>
</tr>
<tr>
<td>5.0–Less than 6.0</td>
<td>40 (13.0)</td>
<td>267 (87.0)</td>
</tr>
<tr>
<td>6.0–Less than 7.0</td>
<td>11 (4.5)</td>
<td>232 (95.5)</td>
</tr>
<tr>
<td>7.0 or Greater</td>
<td>67 (6.3)</td>
<td>998 (93.7)</td>
</tr>
</tbody>
</table>

#### Tumor Size (cm) vs. No. Clear Cell (%) vs. No. Papillary (%) vs. No. Chromophobe (%)

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>No. Clear Cell (%)</th>
<th>No. Papillary (%)</th>
<th>No. Chromophobe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–Less than 1.0</td>
<td>11 (25.6)</td>
<td>32 (74.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1.0–Less than 2.0</td>
<td>79 (59.9)</td>
<td>51 (38.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>2.0–Less than 3.0</td>
<td>186 (70.2)</td>
<td>69 (26.0)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>3.0–Less than 4.0</td>
<td>203 (72.0)</td>
<td>69 (24.5)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td>4.0–Less than 5.0</td>
<td>268 (80.2)</td>
<td>47 (14.1)</td>
<td>19 (5.7)</td>
</tr>
<tr>
<td>5.0–Less than 6.0</td>
<td>218 (82.0)</td>
<td>40 (15.0)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>6.0–Less than 7.0</td>
<td>192 (83.5)</td>
<td>30 (13.0)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>7.0 or Greater</td>
<td>813 (83.0)</td>
<td>98 (10.0)</td>
<td>68 (7.0)</td>
</tr>
</tbody>
</table>
SRMs: current treatment strategies

- Active Surveillance
- Ablative treatments: cryo or radiofrequency ablation
- Nephron sparing surgery: open, laparoscopic: **standard of care**
- Radical Nephrectomy: should be considered as an **over treatment**
Unmet needs in RCC diagnosis

- The incidence of SRMs is dramatically increasing due to the widespread use of abdominal imaging

- The natural history of SRM needs to be further studied
  - Risk of over-treatment in case of benign or low aggressive tumors
  - NSS still uncommon even for the smallest renal masses (20% for tumors measuring 2 to 4 cms)
  - Cystic RCCs are not well diagnosed by conventional CT

- We currently rely only on CT ±Tumor biopsies

- There is a clear need to improve our diagnosis armamentarium in order to better define treatment strategies

Miller et al., J Urol 2006
potential for new solutions with CAIX imaging
Carbonic Anhydrase IX (CAIX)

CAIX is an hypoxia downstream gene coding for a transmembrane glycoprotein (cell surface receptor). Constitutively upregulated in up to 95% of clear-cell renal cell carcinomas (ccRCC). Rarely expressed by indolent RCCs (papillary, chromophobe RCCs). Not expressed in benign tumours and normal tissue (except low level expression in GI tract).

Girentuximab (cG250) specifically binds to CAIX Ag and is specific for ccRCC.
Development of 124 Iodine girentuximab(CAIX) PET/CT Concept

- Early studies in Nijmegen with $^{131}$I-cG250 showed excellent specific tumour targeting
  - Primary renal tumour and metastases visualised with radioscintigraphy

- Concept of using $^{124}$I-labelled cG250 (USAN: Iodine I 124 girentuximab) developed by MSKCC/LICR

- Positive proof-of-concept study performed 2005-2006
  - Ability to detect ccRCC malignancies pre-operatively confirmed

- Pivotal study protocol (REDECT) developed with FDA input
  - SPA approved by FDA
Proof of concept study: CAIX PET/CT images

Iodine I 124 girentuximab adds biological information to anatomical information

Divgi et al, Lancet Oncol. 2007; 8: 304-10
Proof of concept study performed at MSKCC

**Study details**
- Monocenter trial, performed Jun 05 – Mar 06
- 26 patients with renal mass scheduled for surgery
  - 25 patients evaluable
- PET/CT scan using Iodine I 124 girentuximab prior to surgery
- Histopathology as standard of truth

**Major study results***
- Sensitivity: 94% (95% CI 70-100%)
- Specificity: 100% (95% CI 66-100%)

**Limitations**
- Monocenter-study
- Limited to PET/CT scanner with 2D-image reconstruction used
- Low number of histological subtypes

*Results to be investigated in adequately powered confirmatory Phase III trial*  
*Divgi et al, Lancet Oncol. 2007*
REDECT Study Essentials

- Trial to investigate detection of ccRCC by PET/CT using Iodine I 124 girentuximab
- 5mCi/10mg Iodine I 124 girentuximab
- Standard of truth = histopathology
  - Central pathology read, 1 blinded reader
- 2 diagnostic methods to be compared: CAIX PET/CT vs CT
  - Central image read by 3 blinded readers per imaging modality
  - Binary read (ccRCC or no ccRCC)
- 14 sites in the US enrolled patients
- PET/CT and CT scanners of all major manufacturers

Study results will be presented at the AUA meeting, San Francisco, 1Jun 2010
CAIX PET/CT as an upfront diagnosis imaging modality in SRMs?

- CAIX positive SRMs
  - Patient suitable for surgery → NSS
  - Patient non suitable for surgery → Ablative techniques

- CAIX negative SRMs
  - Patient suitable for surgery → tumor biopsy → NSS or expectant follow-up
  - Patient non suitable for surgery → expectant follow-up

Could avoid useless biopsies and/or surgical procedures
CAIX PET/CT as a potential useful diagnostic tool in Atypical Renal Cysts

- **Type I:** simple cyst, hydric density (10-20HU) (100% benign) → No place for CAIX imaging

- **Type II:** atypical cyst (thin septa, thin calcifications, hyperdense cyst (>50HU), absence of contrast enhancement (<10HU)
  - Type IIF (F: follow-up)
  - CAIX Imaging: negative → no follow-up; positive → NSS

- **Type III:** Numerous septa, thick wall, thick calcifications, enhancement of septa or cystic wall, surgery is advised: (50% malignancy)
  - CAIX Imaging: negative → expectant follow-up; positive → NSS

- **Type IV:** Cystic cancer: thick and irregular wall, containing enhancing soft-tissue components. Surgery is mandatory (100% malignancy) → No place for CAIX imaging
Future perspectives for 124 Iodine girentuximab PET/CT

- TKI therapy monitoring + metastasis detection
- Control optimal duration of targeted therapies in metastasized patients
- Switch to alternative treatment regimen if necessary
- Study will be initiated later in 2010
- Confirm success of ablation strategies

1 cycle Sunitinib
2 cycles Sunitinib