Tools to evaluate tumour response to therapy:
Imaging
Esmo, Madrid, 2014

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Beaujon Hospital, Clichy, Paris, France
2013-14: What’s new

- Pre-treatment imaging
- Response to therapy
1. Pre-treatment imaging

- To predict tumor response to treatment
- Usual findings: size, extension
- New findings: enhancement, perfusion
1. Pre-treatment imaging

**Neuroendocrine Tumor Liver Metastases:** Use of Dynamic Contrast-enhanced MR Imaging to Monitor and Predict Radiolabeled Octreotide Therapy Response

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**Purpose:** To evaluate dynamic contrast-enhanced (DCE) magnetic resonance (MR) imaging for monitoring and assessing treatment response in patients with neuroendocrine liver metastases treated using yttrium 90 (90Y)-labeled octreotide (90Y-DOTATOC).

**Conclusion:** DCE MR imaging may be used to monitor the effects of peptide receptor radiolabeled targeted therapy in patients with neuroendocrine tumors liver metastases; a lower pre-treatment distribution volume and high arterial flow fraction was associated with a better response to treatment.

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Neuroendocrine Tumor Liver Metastases: Use of Dynamic Contrast-enhanced MR Imaging to Monitor and Predict Radiolabeled Octreotide Therapy Response¹

- Baseline Parameter Comparisons Found to Be Different Between Responders and Nonresponders ($P < .05$)

*Calculated with the Mann-Whitney $U$ test.*
1. Patients who responded to the treatment were found to have significantly higher baseline arterial flow fraction compared with those who did not respond.

Figure 2: Example parametric maps from a patient in the responder group, showing baseline and post-treatment images.

Figure 4: (a) Kaplan-Meier curves by using multiparametric approach. Blue curve = responders with both ADC and arterial enhancement (ADC ≥ 15% and enhancement ≥ 25%). Median survival was 41 months. Green curve = nonresponders with both ADC and arterial enhancement (ADC < 15% and enhancement < 25%). Median survival was 15.5 months. Red curve = patients who demonstrated either ADC or arterial enhancement response (ADC ≥ 15% or enhancement ≥ 25%). Median survival was 15 months (log-rank test, P < .003).
2013-14: What’s new

• Pre-treatment imaging

• Response to therapy
2.1 PFS predictors MRI baseline

Defining predictors for long progression-free survival after radioembolisation of hepatic metastases of neuroendocrine origin

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Abstract

Results Median PFS was 727 days (95 % CI, 378–964). In the univariate regression analysis, hypovascular metastases progressed earlier (111 vs 727 days; $P<0.05$). Age, sex, and range (10–76) were unrelated to progression-free survival. Median Ki-67 was 3–20 % higher than 20 % (911 vs 727 vs 210 days, respectively; $P<0.05$). Low NSE predicted longer PFS (911 vs 378 days; $P<0.05$). In the
2.1 Kaplan–Meier analysis of progression-free survival after radioembolisation. Kaplan–Meier curves were analysed separately for different categorical predictors.
2.2 PFS predictors MRI at 3 months

Towards New Response Criteria in Neuroendocrine Tumors: Which Changes in MRI Parameters Are Associated With Longer Progression-Free Survival After Radioembolization of Liver Metastases?

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Purpose: To evaluate the association of therapy-related changes in imaging parameters with progression-free survival (PFS) of patients with unresectable liver metastases from neuroendocrine tumors (NETLMs).

Materials and Methods: Forty-five radioembolized patients (median age: 62 years; range: 43–75) received a pre- and 3 months posttherapeutic magnetic resonance imaging (MRI) examination. The latter were evaluated for tumor size, arterial enhancement, and necrosis pattern. Influences of therapy-related changes on PFS were analyzed. Statistical analysis included Student’s t-test, Wilcoxon test, Cox regression analysis, and Kaplan–Meier complementary information and are associated independently with long PFS.

Conclusion: A decrease both in sum of diameters and arterial enhancement of metastases, as well as an increase in necrosis, are associated with significantly longer PFS after radioembolization.

Key Words: liver metastases; neuroendocrine tumors; radioembolization; progression free survival

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Towards new response criteria in neuroendocrine tumors: Which changes in MRI parameters are associated with longer progression-free survival after radioembolization of liver metastases?

A 74-year-old female patient with extensive liver metastases of neuroendocrine origin.

A,B: Baseline MR images show a hypervascular, centrally necrotic metastasis in the right liver lobe.

C,D: Follow-up images acquired 3 months after radioembolization show a significant decrease in arterial enhancement and an increase in the extent of necrosis.
Towards new response criteria in neuroendocrine tumors:

Kaplan–Meier curves for PFS stratified by changes in imaging parameters between baseline and 3-month followup.

A decrease in sum of diameters, in arterial enhancement, and an increase in the extent of necrosis of metastases showed significant effects on the PFS.
2.3 About these results

- These papers studying contrast uptake and vascularization, take in account necrosis
- RECIST
  - accurate in assessing tumor progression
  - inaccurate in assessing tumor response after locoregional therapy or under molecular targeted therapy
- Haesun Choi criteria (CT pattern), which take in account necrosis, show more response with these therapies than RECIST criteria
- The study of contrast uptake is useful to study response to treatment

Choi, J Clin Oncol 2007
Faivre, Clin Can Res 2011
Examples of discrepancies between methods of evaluation:

CT Baseline

- **RECIST**
  - Stable

- **CHOI criteria**
  - Response

Baseline

- **Response**

- **Progression**
2.3 Should we abandon RECIST?

- No, RECIST is used in many clinical trials

- Tumours cells are destroyed by cytotoxic agents: shrinkage a suitable endpoint for measuring biological activity of the drug

- And RECIST is part of H Choi criteria

- It is suggested to keep RECIST 1 thresholds: 30% and 20%
  - And add changes in density of H Choi criteria
## 2.3 ENETS-Modified criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR*</td>
<td>Disappearance of all lesions</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td>PR*</td>
<td>A decrease in size of 30% or a decrease in tumor density (HU) of 15% on CT</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>No obvious progression of non measurable disease</td>
</tr>
<tr>
<td>SD*</td>
<td>Does not meet the criteria for CR, PR, or PD</td>
</tr>
<tr>
<td>PD</td>
<td>An increase in tumor size of 20% and does not meet criteria of PR by tumor density (HU) on CT</td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
</tr>
</tbody>
</table>

- Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield Unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.

The sum of longest diameters of target lesions as defined in RECIST 1.
What about Diffusion MRI?
2.4 DW-MRI patterns and ADC

b0  b150  b800  ADC b0,800

Tumor, Cyst, necrosis
2.4 Diffusion-weighted imaging can evaluate perfusion of metastases: IVIM

IVIM : Intra Voxel Incoherent Motion

Many studies have shown that diffusion curves are made of 2 portions, the perfusion components being studied by low b
2.4 IVIM, perfusion effect and $b_{0,50}$

$$S = S_0 [(1-f) \cdot \exp(-b \cdot D_r) + f \cdot \exp(-b(D_r + D^*))]$$
2.4 Diffusion-weighted imaging can evaluate perfusion of metastases: IVIM

Evaluation of perfusion and diffusion components requires fractionned apparent diffusion coefficients (ADCs). Their values are calculated with multiple b, usually b0, b50, b 150, b 800 ....

This perfusion effect represented by apparent diffusion coefficient, ADC (0, 50) can be measured in NET metastases

It is called IVIM
Conclusions Our study showed that the ADC (0,50) is a promising biomarker for response assessment of neuroendocrine liver metastases following SIRT.

ADC (0,50), IVIM, is reflecting the perfusion factor of the tumor.

Once again the high perfusion of liver metastases is a good pronostic factor of response to treatment.
2.5 Diffusion-Weighted imaging can evaluate response to therapy of metastases

Apparent diffusion coefficient (ADC) measurements as very early predictive markers of response to chemotherapy in hepatic metastasis: A preliminary investigation of reproducibility and diagnostic value
Filip Deckers MD1,*, Bert De Foer MD, PhD1, François Van Mieghem MD1, Thomas Botelberge MD2, Reinhilde Weytjens MD3, Anwar Padhani MD, PhD4 and Marc Pouillon MD

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- DW-MRI with ADC: Diffusion weighted magnetic resonance imaging with apparent diffusion coefficient
2.5 ADC measurements as very early predictive markers of response to chemotherapy in hepatic metastasis

Responder.

ADC map before therapy

a: shows low ADC values (846 × 10 m/s) with central necrosis as an internal area of high ADC.

b: at 12 days after the start of therapy, an increase in ADC can be seen (1217 × 10 m/s) (b).

Corresponding CT scans

c: before and

d: 3 months after (d) therapy confirm lesion response.
2.5 ADC measurements as very early predictive markers of response to chemotherapy in hepatic metastasis

Nonresponder.

ADC map before therapy.

a: The outlined metastasis has an ADC value of $935 \times 10$ m/s.

b: At 12 days after the start of therapy, no change in ADC is seen ($986 \times 10$ m/s).

Corresponding CT scans

c: before and
d: 3 months after therapy depicting disease progression.
2.5 ADC measurements as very early predictive markers of response to chemotherapy in hepatic metastasis

- They would have predicted 7/8 nonresponders correctly.
- However, 6 of 12 responding patients would have been falsely classified as nonresponding to their treatment.

- The study suggests that if DWI of the liver is to be used for decision making early after starting therapy for metastatic liver disease, then data acquisitions need to be made more robust and reproducible.
Conclusions

• Recent data concerning liver metastases are focused upon vascularisation of the lesions

• And try to predict response to therapy

• Hypervascular metastases responder better to treament

• If the vascularisation of treated lesions decreases, the biological response and/or survival are higher