MOLECULAR IMAGING: CONTRIBUTION TO PERSONALISED ONCOLOGY

Molecular imaging biomarkers in solid tumours

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WHAT IS MOLECULAR IMAGING?

Imaging of molecular/metabolic processes:
- glucose metabolism: $^{18}$F-Glucose (FDG)-PET
- amino acids: $^{18}$F-Ethyl-Tyrosine (FET)-PET
- hypoxia: $^{18}$F-Misonidazole (FMISO)-PET
- proliferation: $^{18}$F-Thymidine (FLT)-PET
- …

Imaging of molecular targets:
- Oestrogen receptors: $^{18}$F-Estradiol (FES)-PET
- Somatostatin receptors: ie $^{68}$Ga-DOTATATE-PET
- Prostate-Specific Membrane Antigen (PSMA): $^{68}$Ga-PSMA-PET
- …

Images Courtesy of Institut Jules Bordet

Dual molecular PET imaging: patient with pancreatic NET G2 showing mismatch between SSTR expression (DotaTATE PET) and metabolic activity (FDG PET)
EXAMPLES OF DUAL MOLECULAR IMAGING

Recurrent prostate cancer

Patient with prostate cancer showing no mismatch between expression of PSMA (Prostate Specific Membrane Antigen) and metabolic activity (FDG): all FDG-positive lesions express PSMA.

PSMA PET/CT provides image of disease extent (Staging) whereas FDG-PET/CT provides a grading of the disease (i.e. amplification of glycolytic activity of the tumour is a sign of malignant transformation coupled to infaust prognosis).

Images Courtesy of Institut Jules Bordet
EXAMPLES OF DUAL MOLECULAR IMAGING

Drug target imaging

Patient with metastatic breast cancer, showing no FDG uptake and a positivity for FES PET. Disappearance of FES-positive lesions after treatment by SERD (selective oestrogen receptor degrader)

FES PET shows the target expression for targeted therapy

Images Courtesy of Institut Jules Bordet
WHY DO WE NEED BIOMARKERS IN MODERN ONCOLOGY?

Need of biomarkers predictive of the presence of a drug target and predictive of response to therapy

Molecular imaging could help personalise oncological care by providing tools able to identify the patients *unlikely to benefit* from a targeted treatment:

1. by detecting a drug target’s presence/absence
2. by identifying the non-responding patients early after the therapy onset

Molecular imaging provide additional prognostic information on tumour stage & grade (FDG-PET) and burden (Metabolic Active Tumour Volume (MATV))
ROLE OF METABOLIC IMAGING: PREOPERATIVE STAGING

FDG PET's currently accepted indication: exclude distant dissemination in case of locoregional advanced gastro-esophageal cancer (Tumour cartography)

Images Courtesy of Institut Jules Bordet
ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

Use of dual metabolic imaging to define NENS phenotype

Ileal GEP-NET grade I

Lung NET grade 3

Duodenal NET grade 1

Ileal tumour (red) & liver M+ (blue) express SSTR2 No avidity for FDG

Lung tumour (red) & liver M+ (blue) don’t express SSTR2 but are avid for FDG

Intestinal tumour (red) & liver M+ (blue) express SSTR2 and some liver lesions are avid for FDG, without mismatch

Images Courtesy of Institut Jules Bordet
ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

Use of dual metabolic imaging: the PET score

Pathological grade (ENETS)

G1: Ki-67 <2%
G2: Ki-67 2-20%
G3: Ki-67 >20%

Dual PET (FDG- and Octreo-PET) Imaging score

C1: all lesions OctreoPET+ & FDGPET-
C2: all lesions OctreoPET+ some FDGPET+
C3: mismatch of at least 1 lesion FDGPET+ is OctreoPET-

Dual PET-based imaging score seems to allow better classification of outcome as compared to classical pathological grade

This research was originally published in JNM, Karfis I, et al. J Nucl Med May 1, 2019 vol. 60 no. supplement 1 1523. © SNMMI.
http://jnm.snmjournals.org/content/60/supplement_1/1523
ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

Defining hepatocellular carcinoma phenotype

FDGPET as a prognostic factor for recurrence after liver surgery¹

FDGPET as a independent prognostic factor for recurrence after liver transplantation²

High negative prognostic value of FDGPET in HCC

(1) Reprinted from HPB Journal, 21(6), Lim C, et al. 18F-FDG PET/CT predicts microvascular invasion and early recurrence after liver resection for hepatocellular carcinoma A prospective observational study, 739-747., Copyright (2019), with permission from Elsevier. 2. Kornberg A, et al. Sci Rep 2017: 14176 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License.
ROLE OF METABOLIC IMAGING: PROGNOSIS ASSESSMENT

Baseline Metabolically Active Tumour Volume (MATV) as a prognostic biomarker

Examples of patients with diffuse large B-cell lymphoma with low baseline MATV (<300 cm³); patients A and B, and patients with high MATV (>300 cm³); patients C and D.

Reprinted (or adapted) from Clinical Cancer Research, 2016, 22(15), 3801-9, Cottereau A-S, et al. Molecular Profile and FDG-PET/CT Total Metabolic Tumor Volume Improve Risk Classification at Diagnosis for Patients with Diffuse Large B-Cell Lymphoma, with permission from AACR.
Role of Metabolic Imaging: Prognosis Assessment

Metabolically Active Tumour Volume (MATV) at baseline defines prognosis in metastatic chemorefractory colorectal cancer.

This research was originally published in JNM. Woff E, et al. J Nucl Med 2019;60(10):1366-72. © SNMMI. http://jnm.snmjournals.org/content/60/10/1366. .
ROLE OF METABOLIC IMAGING IN RESPONSE PREDICTION
Dynamic information during therapy

1. Tissue metabolic activity is affected in damaged cells before their death leads to changes in tumour size
2. A treatment that does not induce tumoural metabolic changes will probably not lead to a significant tumoural shrinkage

There is a current international standardisation effort leading to improved usability of metabolic imaging response assessment for clinical and research purposes.

Early (after 1 CT course) FDG-PET/CT-based metabolic response assessment has a high negative predictive value on pathological response.

Table 3. Accuracy of Early Metabolic Response Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Histopathologic Response</th>
<th>Clinical Response</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
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<tr>
<td>Positive predictive value</td>
<td>8/18</td>
<td>44</td>
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<tr>
<td>Sensitivity</td>
<td>8/10</td>
<td>80</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>36/38</td>
<td>95</td>
</tr>
<tr>
<td>Specificity</td>
<td>36/46</td>
<td>78</td>
</tr>
<tr>
<td>Accuracy</td>
<td>44/56</td>
<td>79</td>
</tr>
</tbody>
</table>

METABOLIC RESPONSE ASSESSMENT (MRA)
In Locally Advanced Solid Tumours – Oesophageal Cancer (2/2)

MUNICON trial

- No histological response in PET non-responders
- Early Assessment of response may induce rapid treatment reorientation (i.e., stop useless CT and advance curative-intent surgery)

Reprinted from The Lancet Oncology, 8(9), Lordick F, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial, 797-805, Copyright (2007), with permission from Elsevier.
Early MRA defines 2 subgroups of patients with significantly different outcomes under treatment.

MR Heterogeneity-based classification

Class I  All lesions respond
Class II  Most lesions respond
Class III Most lesions do not respond
Class IV No lesion respond, or new or progressive lesion

About 50% of diseases show heterogeneity in response with coexisting responding and non-responding lesions, prompting a descriptive classification

Patients with homogeneous metabolic response have a significantly improved prognosis as compared with patients with at least one non-responding lesion.
Outcome according to metabolic response (mR) in advanced chemorefractory colorectal cancer

Combined analysis of 2 studies: SoMore (NCT01290926) & RegARd-C (NCT01929616)

Patients with homogeneous metabolic response have a significantly improved prognosis as compared with patients with at least one non-responding lesion

METABOLIC RESPONSE ASSESSMENT

In metastatic setting – metastatic colorectal cancer

Outcome according to metabolic response & baseline MATV

Combined analysis of 2 studies: SoMore (NCT01290926) & RegARd-C (NCT01929616)

Both pre-therapeutic metabolic assessment of tumour burden (MATV) AND dynamic metabolic assessment of response after 1 treatment course independently predict the outcome of patients

Several candidates for immuno-imaging biomarkers:

- Granzyme B PET (intratumoural immune activation?)
- Anti-PDL1-PD1 PET (Target of Anti-PDL1-PD1 therapies)
- …
PERSPECTIVES: MOLECULAR DRUG TARGET IMAGING
In immunotherapy – $^{89}$Z-atezolizumab PET Scan

PERSPECTIVES: THERANOSTICS IN NUCLEAR MEDICINE

Using the same tracer (vector) for both **Molecular Imaging** and radionuclide therapy (**Molecular Radiotherapy**)

**Neuroendocrine tumours**
- **Somatostatine Receptor**
  - Diagnosis: Ga68-DOTA-octreotate
  - Therapy: Lu177-DOTA-octreotate (PRRT)

**Prostate cancer**
- **Prostate Specific Membrane Antigen**
  - Diagnosis: Ga68- PSMA ligand
  - Therapy: Lu177- PSMA ligand
Example: PRRT (Peptid Receptor Radionuclide Therapy) for NET’s

Baseline Octreo- (left) & FDG- (right) PET/CT June 2013

Octreo- (left) & FDG- (right) PET/CT post 4 $^{177}$Lu-DOTATATE Sept 2014 (complete remission)

Images Courtesy of Institut Jules Bordet
Molecular Imaging will deeply impact on management of solid tumours, both as a screening and as a monitoring tool

1. Screening tool
   - define disease extension (stage) before curative-intent surgery
   - define disease burden (MATV) as prognostic indicator
   - define disease biology (FDG avidity as a prognostic indicator ie. NET, HCC)
   - define presence of molecular targets (eg. FES-PET), eventually related to theranostics (Octreo-PET, PSMA-PET)

2. Monitoring tool
   - assess (FDG-based metabolic response) likelihood to benefit from chemotherapy earlier than RECIST
   - in the near future Molecular Imaging might become able to assess response to immunological agents
     - Granzyme B PET/CT (intratumoural immune activation?)
     - Anti-PDL1-PD1 PET/CT (drug target imaging)
THANK YOU!
DISCLOSURES

- Alain Hendlisz has reported no conflict of interest
- Patrick Flamen has reported no conflict of interest