Selective Internal Radiation Therapy (SIRT) in the multimodal approach to Hepatocellular Carcinoma

International Course on THERANOSTICS and MOLECULAR RADIOTHERAPY

Brussels, 4 October 2017

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Background

• Hepatocellular carcinoma (HCC) is the 5th most frequent cancer in men and the 7th in women

• Second leading cause of cancer-related deaths worldwide

• Closely associated with chronic liver disease (cirrhosis)

• Multifocality (cirrhosis as a precancerous condition)

• Most of the patients are not amenable to curative-intent treatments

World Health Organization. Mortality database. [http://www.who.int/whosis](http://www.who.int/whosis)
The therapeutic challenges in HCC

- Dual pathology, tumor and cirrhosis
- Heterogenicity of the disease
- Poor tolerance to surgery
- Poor chemosensitivity, poor tolerance to systemic treatments
- High relapse rate after local treatment
- Liver transplantation is the best therapeutic option but dramatically limited by organ shortage
Locoregional Transarterial Therapies for HCC

Transarterial Chemoembolization (TACE)
Intra-arterial infusion of chemotherapy and proximal embolization
Ischemic-cell death

Selective Internal Radiotherapy (SIRT)
Distal intra-arterial infusion of $^{90}$Yttrium microspheres, no macro-embolic effect
Radiation-induced cell death

Tumor necrosis
Tumor downsizing
Disease control
Locoregional intra-arterial therapies in HCC

The need to categorize the patients:

• Barcelona Clinic Liver Cancer (BCLC)
  – Stage 0-A (early): single tumor <2 cm (0), single tumor<5 cm or ≤3 tumors ≤3 cm (A) (Milan criteria)
  – Stage B (intermediate): single >5 cm, 2-3 tumors with at least 1 >3 cm, or >3 tumors
  – Stage C (advanced): macrovascular invasion (portal, SHV, IVC)
• CHILD-PUGH
• MELD
• Portal HT
• AFP scores...
The selection of the individual treatment

• Both HCC and cirrhosis have extremely heterogenous behavior
• BCLC or CHILD or MELD scores do no reflect this heterogeneity
• Need for new **biomarkers** for individual tumor biological characteristics
  – FDG PET scan (1, 2)
  – Biopsy (differentiation, microvascular invasion) (3, 4)
  – Blood inflammation scores (5)
  – Intra-tumor immune infiltrates (6-9)
  – Response to treatment(s) ...

SIRT in the multimodal approach to HCC Consensus, Guidelines

As an alternative to TACE,

• As a bridging treatment in early stage or main therapy in patients with diffuse intrahepatic spread (ESMO guidelines) (1)

• For patients with unresectable disease (diffuse, inadequate hepatic reserve, poor PS, location/extension of the tumor) (National Comprehensive Cancer Network) (2)

• In selected patients with liver-only HCC, not eligible for LT or resection (National Cancer Institute) (3)

However,

• Relatively recent introduction

• Very few RCT data ...

2. NCCN 2015
SIRT in the multimodal approach to HCC
The evidences and recommendations
## Therapeutic decision in HCC

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<td>C</td>
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<tr>
<td>Standard therapy</td>
<td>Transplantation</td>
<td>TACE ± sorafenib</td>
<td>Sorafenib</td>
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<tr>
<td>Therapeutic objective</td>
<td>Cure ↓ post-Tx recurrence</td>
<td>OS PFS</td>
<td>OS QoL</td>
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<tr>
<td>Objective for intra-arterial therapy</td>
<td>As bridging therapy: To control before Tx ↓ post-Tx recurrence</td>
<td>To control the disease (OS, PFS, QoL) Conversion to surgery (→ Cure)</td>
<td>To limit progression (OS, PFS, QoL)</td>
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# Therapeutic decision in HCC: SIRT versus Standard therapy

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<td>Treatment objective</td>
<td>As a bridge to transplant: ↑ rate of cure</td>
<td>OS PFS</td>
<td>OS QoL</td>
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<td>SIRT vs standard</td>
<td>(Very few data)</td>
<td>↑ PFS (?) No benefit on OS Cost Conversion to surgery</td>
<td>No benefit on OS Tolerance Cost</td>
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<td>- Feasible</td>
<td>- May increase RR, CPR</td>
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SIRT versus Sorafenib in advanced inoperable HCC

**SARAH trial** (V. Vilgrain) Randomised, controlled, open-label, multicentre investigator initiated Phase 3 trial.

SIRT versus Sorafenib (n=459, locally advanced inoperable HCC)

*primary endpoint : OS*

- Median OS: 8.0 months versus 9.9 months (p=0.179).
- Radiologic progression significantly ↓ in SIRT group (p=0.014)
- Response rate significantly higher in the SIRT group (19.0% vs 11.6%, p=0.042).
- Improvement of side-effect profile and QoL in SIRT (p=0.005).
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SIRT versus TACE in intermediate HCC

1 RCT (Salem. Gastroenterology 2016)
BCLC A and B, Y90 (n= 24) versus TACE (n=21)

- ↑TTP (>26 months vs 6.6 months, p=0.0012)
- ↓side effects
- Similar response rates
- Similar median survival
SIRT for HCC

• Effective (response rate: 50-70%, CRR or CPR: 30-90%)
• Feasible in case of PVT
• Favorable safety profile
• High cost

→ **Predictability** : Avoidance of toxic/useless treatments
→ **Conversion** to surgery

Rationale for SIRT before partial hepatectomy

• **To improve selection:**
  – Tolerance to SIRT as a marker of functional liver reserve
  – Response to SIRT as a marker of tumor biology
• **To improve resectability:**
  – Tumor downsizing (surgical radicality, parenchyma-preserving resection)
  – Liver volumes modulation
• **To improve curability:**
  – SIRT to modify tumor immune microenvironment
SIRT before partial hepatectomy for HCC

Questions

1. Feasibility of PH after SIRT ?

2. Liver volumes modulation ?

3. Effects of SIRT on tumor immune microenvironement ?
Partial Hepatectomy for HCC

PH could be curative in highly selected patients

Excluding salvage LT,
For tumor < 5 cm
5-Y OS: 57%
5-Y DFS: 32%
Kluger. J Hepatol 2015

In highly selected patients:
Second hepatic resection for recurrent HCC i
Mean time to re-resection:
2 years
5-Y OS: 67%
Roayaie. J Hepatol 2011
Feasibility of PH after SIRT

• Clinical series/observations indicate the feasibility and safety of post-SIRT liver resection
• Reported problems of:
  – Adhesions and bleeding
  – Inflammation/fibrosis
  – Endothelial damages and related portal hypertension
  – Higher blood loss
• No excess mortality

The Post-SIR-Spheres Surgery Study (P4S): Retrospective Analysis of Safety Following Hepatic Resection or Transplantation in Patients Previously Treated with Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres

- Retrospective international multicentre study to assess outcomes of liver resection or transplantation following SIRT
- 71 liver resections including 22 for HCC
- No excess morbidity and mortality
- No operative death attributable to preoperative SIRT

F Pardo et al. Ann Surg Oncol 2017
SIRT to modulate liver volumes

- Radiation lobectomy
- Combining tumoricidal effect
- As an alternative to portal vein embolization:
  - Tumor growth in the embolized sector
  - New micrometastases in the FRL

Sandri. Hepatobiliary Surg Nutr 2017
Clinical case

- 73 years old man
- Alcohol-reated CHILD A cirrhosis
- 40 mm S4 HCC
- Therapeutic plan:
  1. SIRT
  2. Left hepatectomy
Clinical case

TLV : 2339 cc
FRLV : 1527 cc (65%)
FRLV/BW : 0.68
Clinical case: Arteriography

Left hepatic artery from right gastric artery
tumor blush
non tumor left liver from gastroduodenal artery
Clinical case: Post-SIRT 90Y PET

tumor distribution of Y90 (161 Gy)  
non tumor left liver distribution of 90Y (120 Gy)  
28 days later
Clinical case: Post-SIRT MRI (d110)

FRV: 1648 cc (75%, previously 65%)
Clinical case: Left hepatectomy (S5) (d115)
Effects of SIRT on tumor immune microenvironment

Hypotheses

• Radiation-induced cell death may trigger local immune response

• Local attraction/activation of effector cytotoxic T cells may participate to the tumoricidal effect of SIRT

• Enhancement of anti-tumor immune response may promote a systemic effect \textit{abscopal-like effect} \rightarrow micrometastases

• Stimulation of immune memory response \rightarrow relapse
Effects of SIRT on tumor immune microenvironment

• Retrospective study to analyze immune cellular infiltrate in patients operated for HCC:
  – without preoperative treatment
  – after TACE
  – after SIRT

ImmunoHisto Chemistry
CD3, CD4, CD8, CD20, GZB

Ligia Craciun
Tumor infiltrating T cells

SURG (n = 32)
SIRT (n = 12)
TACE (n = 16)

*P < 0.02

**P < 0.0086

*P < 0.03

Ligia Craciun
no preoperative treatment  
preoperative SIRT

CD4+ in brown  
CD8+ in red

Ligia Craciun
Intra-tumor Granzyme B expression

Ligia Craciun
Conclusions

• SIRT is an effective treatment for HCC
  – No clear benefit versus TACE as a bridge to transplant
  – No clear benefit versus sorafenib in advanced stages

• Key advantages
  – Tolerance
  – **Predictability** → avoidance of toxic and/or useless treatments

• Main disadvantage
  – Cost
Perspectives

• SIRT in a preoperative setting
  – To improve resectability and curability
  – As an alternative to PVE (+ tumoricidal effect)
• To modulate anti-tumor immune response:
  – To promote local anti-tumor effector mechanisms
  – To promote systemic tumor-specific immune response (vaccinal effect)
  – In combination with immunotherapy
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