Normal Liver Toxicity

- RILD is a limiting factor for high dose RT of intrahepatic cancers
- Clinical complications usually present 2-6 weeks after the completion of therapy, with devastating outcomes
- Radiation-induced tissue toxicity is a complex, dynamic and progressive process
- Individual sensitivity to radiation limits the utility of existing NTCP models
- Determination of specific risks versus benefits of treatment should be an integral part of clinical decision making for each patient

Functional Imaging

- A valuable tool for evaluation of normal tissue toxicity
- Temporal changes in normal tissue from pre to during and to post RT
- Spatially-resolved volumetric distribution of function of subunits
- Individual sensitivity to dose
- Pre-RT dysfunction of the live or functional reserve
- Early assessment and prediction of potential radiation risks and clinical outcomes
- Re-optimization of individual patients' treatment plans and early intervention involving tissue/organ protection

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Liver Functional Imaging

- Hepatic perfusion imaging (DCE MR and CT)
  - Arterial and portal venous perfusion
  - Histopathology of RILD is venous occlusion
- $^{99m}$Tc HIDA SPECT
  - Hepatic extraction fraction and biliary function
- Eovist MRI
  - Hepatic extraction fraction and biliary function
- $^{99m}$Tc galactosyl serum albumin (GSA) scintigraphy or SPECT
  - Hepatocyte binding via the asialoglycoprotein receptor (Schneider, Surg clin N Am 2004)
- $^{18}$F-Deoxy-Galactose (FDGal) PET
  - High uptake in tumor cells
  - Dose response in normal liver (Hoyer, ESTRO 2011)
Hypotheses

> Changes in portal venous perfusion and/or hepatobiliary function during the early course of RT are potentially a biomarker for liver dysfunction after irradiation
> Perfusion and/or hepatobiliary function biomarkers may allow us to select patients who are susceptible to liver injury prior to clinical symptoms and therefore to modify treatment
> Assessment of Individual and spatial sensitivity to doses by functional imaging during the course of therapy allow us to adapt treatment plan to minimize local tissue damage and thereby to prevent from organ injury

Liver Functional Imaging at UM

> Prospective perfusion CT/MRI and HIDA SPECT protocols
> Patients with intrahepatic cancers and treated with RT
> Patients at high risk for liver injury
  - Large tumor volume
  - Primary cancers, e.g., HCC with or without cirrhosis
  - Previous treatments, e.g., TACE, RFA, resection, or RT
> DCE CT/MRI and HIDA SPECT
  - Pre-treatment, mid-course (50-60%), and post RT (1 and 2 months after treatment completion)
  - DCE MRI covers the whole liver
> Overall liver function assessment
  - Indocyanine green (ICG) clearance or retention: the best established test for overall liver function

Venous Perfusion Dysfunction

Prior to RT
After 45 Gy
30 fx of 1.5 Gy/fx twice daily
Cao Y et al., Medical Physics 2007

Dose Effect on Venous Perfusion

After 45 Gy (during RT)
One month after RT

Note: (1) time dependent slopes – time dependent response
(2) Individual variation -- individual sensitivity
Individual Sensitivity to Radiation

- **Y-intercept or low dose region:** reperfusion
- **Slope:** reduction in perfusion caused by unit dose
- **X-intercept:** critical dose resulting in undetectable venous perfusion

\[ y = -0.0423x + 229.7 \]
\[ R^2 = 0.85 \]

![Graph showing Individual Sensitivity to Radiation](image)

Liver Functional Volume

<table>
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<tr>
<th>Patient</th>
<th>Slope (mL/(100 g min) per Gy)</th>
<th>Dose (Gy)</th>
<th>LV% Fp=0</th>
<th>FLV% Fp=0</th>
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</table>

**Overall Liver Function vs Functional Subunits**

- \[ F_p = \frac{1}{\sum w_i \cdot \beta + \alpha} \]
- \[ F_p = \frac{1}{\sum w_i \cdot \beta_{\text{ICG clearance}}} \]

![Graph showing Overall Liver Function vs Functional Subunits](image)
Mean Liver Dose vs Liver Functional Reserve

Volumetric MRI Perfusion

17 patients in this analysis
- 7 Mets, 7 HCC, and 3 cholangio
- 6 with previous treatments (TACE, RFA, SBRT or resection)
- Tx: 5 by SBRT, 12 by fractionated RT

Imaging and liver function tests
- Pre RT, 50%-60% planned doses, 1 and 2 months after RT
- Doses biologically corrected (LQ model w \( \alpha/\beta = 2.5 \)) for different fractional sizes
- Liver function pre RT assessed by ICG clearance
  - 5 pts: \( T_{1/2} > 10 \) min (high risk)
  - 10 pts: \( T_{1/2} \) ranged from 3.7 to 7 min (normal or close to normal)

Mean of Portal Venous Perfusion of Subunits and Overall Liver Function

Changes in Venous Perfusion after RT

\( r = 0.72, p < 1.0 \times 10^{-8} \)
Individual Response Function

Hypoperfusion pre RT and Reperfusion after RT

Four patients:
- Overall Hypoperfusion
  - Mean perfusion in the liver < 60 mL/(100g min)
- Three patients:
  - Overall and regional recovery
  - After RT, except in the highest-dose regions

Cholangio treated by Fx RT

HCC treated with Fx RT

Summary

- Venous perfusion imaging could be a biomarker for local liver function
- There are large variations in dose responses of portal venous perfusion across individual patients and over lobes, segments or regions
- Significant hyperperfusion was observed. The potential relevance for normal tissue sparing/regeneration is worthy of further investigation

99mTc-HIDA SPECT/CT in the Liver

99mTc-HIDA is an established agent for assessment of hepatobiliary function using SPECT.
- Hepatic extraction fraction (HEF)
- Bile excretion rate
Dose Effects on HEF and Bile Excretion Rate

Every Gy causes a reduction:

- 0.67% in HEF when the dose is greater than ~15 Gy
- 0.76% in bile excretion rate

Summary

- Functional and metabolic imaging is emerging as a promising tool for risk management, particularly for patients at high-risk for liver injury.
- Dose-response of liver measured by functional imaging may depend upon treatment regimes.
- Functional/metabolic imaging agent uptake may depend upon enzyme levels in the liver.
- Whether other hepatic functional/metabolic imaging provides any discriminatory information beyond portal venous perfusion has yet to be demonstrated.

Summary

- Our understanding of the histopathology and biologic processes of radiation-induced tissue/organ toxicity is quite limited.
- Functional and molecular imaging are potential biomarkers for early assessment and prediction of radiation-induced tissue/organ toxicity.
- Clinical trials with adequate endpoints are warranted to establish the value of these methods.
Hyperperfusion after liver irradiation → Regeneration?

Kubo, J Hep Res 2002

GSA planar image prior to right portal vein embolization
GSA planar image 2 weeks after right portal vein embolization

Dose-Response of Portal Venous Perfusion

CT
Hepatic Extraction Fraction

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