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# External and Internal Radiation Therapy for Liver Cancer

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## Disclosures

- Research Grants: Elekta, Bayer

## Outline

- Rationale
- External Beam Radiation Therapy
  - Liver metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Liver metastases
  - Hepatocellular carcinoma
  - Most suitable patients

## Outline

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## Rationale: Liver metastases

- Liver metastases from colorectal ca (CRC) and other solid cancers a large source of morbidity and mortality
- Rationale for more liver directed therapies with improved systemic therapies
- Surgery CRC mets: 5 year survival 25 – 50%
  - Long term survival not possible in absence of surgery
- Most patients not suitable for surgery or radiofrequency ablation (RFA)

## Rationale: Hepatocellular Carcinoma

- Sixth most common cancer globally
  - 626,000 cases worldwide annually
  - Increasing globally
- Third cause of global cancer death
  - 598,000 deaths worldwide annually
- ≈ 7% 5 year survival
- Transplant, resection, RFA can cure : 5 year survival 20 – 80%
  - Most patients not eligible for these local therapies

## Hypothesis

- Radiation therapy should improve outcomes in patients with primary and metastatic liver cancer, unsuitable for standard local therapies

ROENTGEN THERAPY OF HEPATIC METASTASES

Brain metastases have for years afforded one of the more striking successes of radiotherapy, but liver metastases have always been regarded as a hopeless proposition, mainly from fear of irreversibly damaging the surviving liver parenchyma.

Phillips, R., Karnofsky, D.A., Hamilton, L.D., Nickson, J.J.: Roentgen therapy of hepatic metastases. *Am. J. Roentgenol.* **71**: 826–834, 1954.

## RT Strategies

- External beam radiotherapy
  - 2D low dose palliative radiotherapy
  - 3D conformal radiotherapy
  - Intensity modulated radiotherapy
  - Stereotactic radiotherapy
  - Protons, Carbon ions
- Brachytherapy
  - Interstitial
  - Interluminal
- Radioisotopes
  - Iodine 131 Lipiodol
  - Yttrium 92 microspheres
- Intra-operative RT (IORT)
  - Mobile electron unit

## Roles of Radiation Therapy

- Palliative (low dose focal / whole liver RT)
  - To delay recurrence
  - To improve symptoms and quality of life
- Radical (tumorcidal/ high focal dose RT)
  - Definitive therapy to improve survival
  - To downstage borderline resectable tumors
  - In conjunction with other liver treatment

## TROG Palliative RT for Liver Metastases

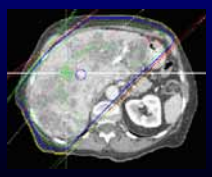
- N=28
- 10 Gy in 2 # over 2 days
- Symptoms:
  - Pain (27)
  - Distension (19)
  - Night sweats (12)
  - Nausea (18)
  - Vomiting (8)
- Premedication: steroid and anti-emetic
- Med survival 10 weeks

## TROG Palliative RT for Liver Metastases

- N=28
- 10 Gy in 2 # over 2 days
- Symptoms scored by MDs (+/- telephone assessment): Symptom scale 0 – 4
  - Symptom response rates: 53-66% at 2 weeks
  - Partial/ complete global symptom responses 54%
- Patient assessment:
  - 12 / 17 “better” on at least 1 occasion

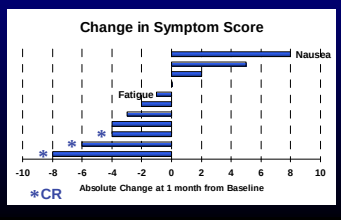
## Palliative RT for liver cancer

- Few studies with QOL and symptom scales
- ≈ 80% pain relief in palliative RT studies for bone or soft tissue metastases
- Ongoing palliative RT study at PMH for symptomatic CRC liver metastases or HCC *
  - 40 patients
  - 8 Gy x 1, 'simple' RT
  - Child A or B
  - Endpoints
    - Symptom improvement
    - QOL



## Symptom Improvement with RT

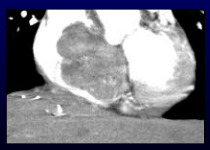
- At 1 month, 3/11 patients had a complete response (CR)
- 7/11 patients - improvement in worst symptom by at least 1 point
- 4/11 patients -no improvement or symptom worsening
- Reduction in 1 mo. symptom score by 1.2 (95% -4.0, 1.5)



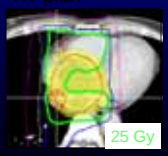

## Palliative RT for HCC portal vein thrombosis

- 47 y. o. man with locally advanced HCC
- Progression post ++ tx (including targeted therapies)
- Symptomatic portal vein, IVC and atrium thrombosis
- RT ant-post pair: 25 Gy in 5#

Baseline CT



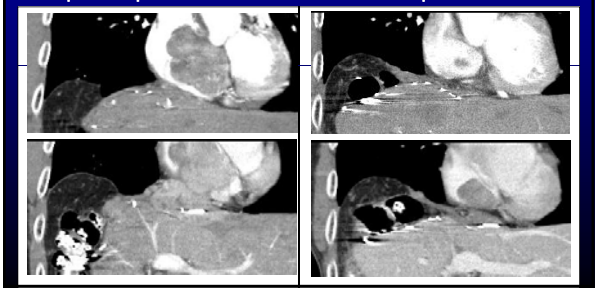
RT plan




## Palliative RT for HCC portal vein thrombosis

- Symptomatic and radiographic response maintained 6+ months post RT

April 07 pre RT | Oct 07 post RT



## What are the challenges in safely using radiation therapy to *radically* treat liver cancers?

## Potential RT Toxicities

- Radiation induced liver disease (RILD)
  - Anicteric ascites
  - Elevated liver enzymes (ALP > AST/ALT)
- Non-RILD hepatic toxicity
  - Elevation of transaminases
  - Reactivation of viral hepatitis
  - Liver decompensation
  - Thrombocytopenia
  - Biliary obstruction
  - Elevated bilirubin
- Non-hepatic
  - Vascular
  - Capsular pain, rib fracture
  - Stomach, bowel bleeding, obstruction, fistula

More common in metastases

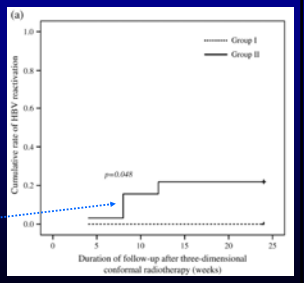
More common in HCC + Hepatitis B

More common with internal RT

More common with external RT

## Hepatitis B reactivation

- Reported after RT for HCC
- Antiviral therapy reduces risk
- Figure
  - Group I antiviral therapy
  - Group II none



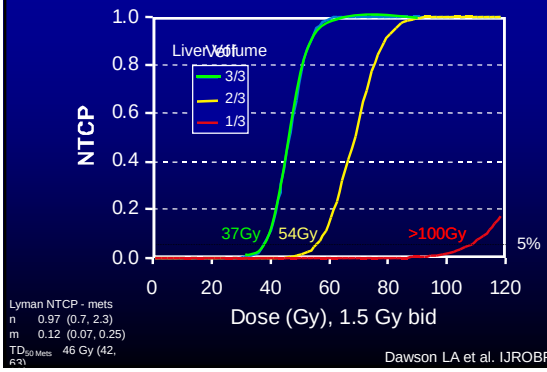

Kim et al. IJROBP 69(3): 813–819, 2007
Center for Liver Cancer, South Korea

## Liver Tolerance – U Michigan

- Series of phase I/II trials since 1987
  - Individualized RT 1.5 Gy twice daily (max 90 Gy)
  - Hepatic arterial FUdR or BUdR
- 203 patients (98 mets, 105 primary); 13 RILD
- Significant multivariate analysis risk factors
  - Male > female
  - BUdR > FUdR chemotherapy
  - HCC > liver metastases
  - Dose and volume of RT delivered

## Liver Tolerance – U Michigan

### Radiation Induced Liver Disease




Dawson LA et al. IJROBP 2002

## Tolerance: Stereotactic Body RT (SBRT)

- SBRT= highly conformal potent dose RT delivered in few fractions (30- 60Gy in 1-10#)
  - Liver toxicity uncommon following SBRT
  - Most SBRT series: <30% effective liver volume irradiated
- 'Safe' liver dose-volume constraints
  - 6 fractions: mean liver dose < 20 Gy
  - 3 fractions: >700 cc < 15 Gy
    D30% < 21 Gy, D50% < 15 Gy
  - 1 fraction: D30% < 12 Gy, D50% < 7 Gy

Dawson, Kavanagh, Wulf, Atca Oncologica 2006

## How to deliver RT safely

- Appropriate patient selection
  - Child-Pugh A > B >>> C
- Technological advances
  - Imaging (tumor and vascular)
  - RT breathing motion management
  - RT planning
  - RT image guidance
  - Interventional radiology technical advances
- Ensure enough residual liver and other critical tissues spared from RT

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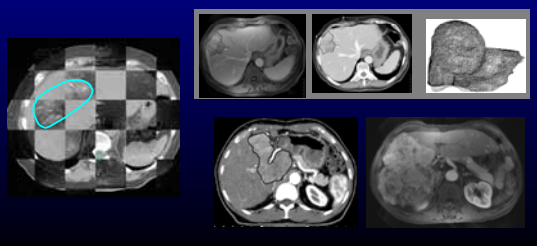
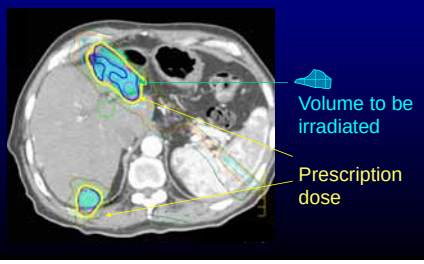
## Imaging

- Multi-modal imaging: CT, MR, US
- Improved spatial and temporal resolution
- Image registration and fusion



## RT Dose Planning

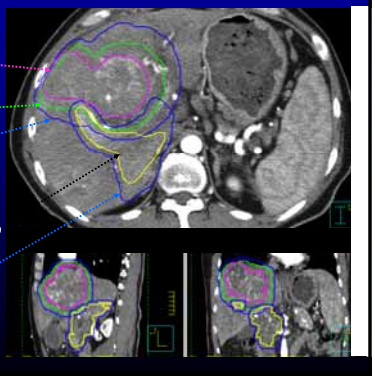
- CT based dose planning with geometric conformation of dose
- Intensity modulated radiation therapy
- Automated computer optimization




## RT Treatment Volumes - HCC

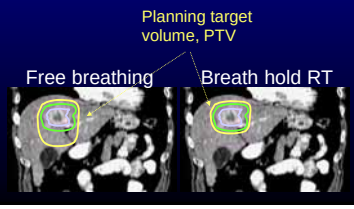
GTV
CTV 5 mm in liver (PMH, Toronto)
PTV (5-30 mm) -individualized

Portal vein thrombus, PVT
PVT CTV 0 mm
PVT PTV



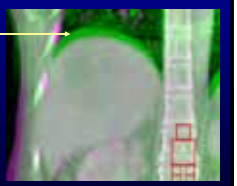
## Breathing Motion Management

- Liver breathing motion measurement tools
  - Fluoroscopy, cine MR, respiratory sorted CT
- Motion management strategies
  - Increase volume irradiated
  - Breath hold
  - Gating beam
  - Track beam




## Image Guided Radiation Therapy, IGRT

- IGRT: Daily imaging immediately before or during RT delivery to position patient more accurately and precisely
- Changes in liver position relative to bones day-to-day
  - Free breathing
  - Breath hold



- IGRT increases likelihood of dose being delivered as planned

## Image Guided Radiotherapy (IGRT)

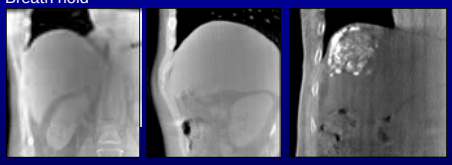

+ integrated systems, MR-linac, …

Dawson, Jaffray, JCO, 2007

## 3D (Volume) and 4D (Temporal) IGRT

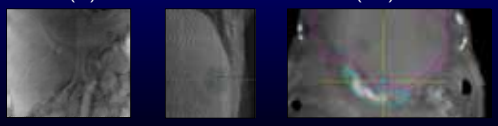
kV Cone Beam CT

Breath hold



Contrast (IV)

Contrast (oral)



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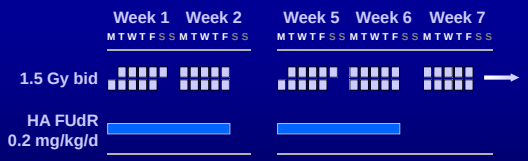
## University of Michigan




- Phase I study, n = 128
- Concurrent hepatic arterial FUdR radiosensitizer
- Individualized prescription dose - based on volume of liver irradiated/ risk of RILD
- Maximum dose 90 Gy, 1.5 Gy/# bid

McGinn C et al. J Clin Oncol. 1998

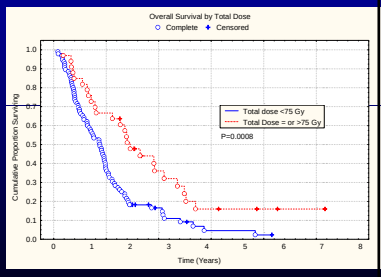
## University of Michigan: Phase I/II

128 unresectable colorectal ca (CRC) liver metastases, HCC or cholangiocarcinoma

Med diameter 10 cm

RT dose:
median 61 Gy
(24-90 Gy)
1.5 Gy fractions
twice daily

47 CRC mets:
med survival 17 mo




Ben Josef E. et al, JCO, 2005

## Toxicity: Michigan, n=123

- Grade 1/2 - 30% (fatigue common)
- Grade 3/4 - 30% (primarily biochemical)
- Grade 5 - 0.8%

- Most common severe complications:
  - Upper GI ulcer and bleeding 5%
  - Radiation induced liver disease 4%
  - Hepatic catheter-related 3%

Ben Josef E et al, JCO, 2005

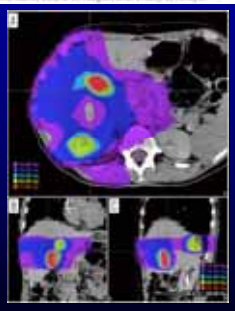
## Trials of Liver Metastases SBRT

| Institution | No. lesions | Fractions | Dose/#, Gy | Med followup, mos | Time | Actuarial LC |
|---|---|---|---|---|---|---|
| **Prospective** | | | | | | |
| Wurzburg | 55 | 1 | 14-26 | 6 | 18m | 67 |
| Aarhus | 141* | 3 | 15 | 4.3 | 2yr | 79 |
| Rotterdam | 45 | 3 | 12.5 | 13 | 2yr | 82 |
| Colorado | 49 | 3 | 20 | 16 | 2yr | 92 |
| Toronto | 140+ ^ | 6 | 5-10 | 11 | 1yr | 70 |
| **Retrospective** | | | | | | |
| Rochester | 293** | 10 | 5 | 41 | 2yr | 67 |

*Total number of colorectal cancer metastases; 44 liver metastases.
**Total number of lesions treated; 45% of patients were treated for hepatic metastases.
‡In surviving patients.
§Different fractionation (3 10 Gy or 5 5 Gy) used for patients with hepatocellular carcinoma or with lesions 4 cm.
^ 68 patients

## Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

- Eligibility, n=46
  - 1-3 liver metastases
  - Solid tumors < 6cm
  - Liver and kidney function OK
    - Bili <3 mg/dL, alb > 2.5 g/dL
    - Liver enzymes <3xULN
    - No ascites
  - No systemic therapy within 14 days pre- or post-SBRT
- Dose escalation to 20 Gy x 3
- Image guidance and breathing motion management
- Liver doses:
  - > 700 cc had to receive < 15 Gy



Rusthoven, J Clin Oncol. 2009.

## PMH Phase I/II Study - Metastases

- Conformal RT for unresectable liver cancer
  - Individualized 'iso-toxic' dose (6 fractions)
  - Breath hold for liver immobilization
- Daily IGRT and repositioning
- 68 patients with metastases (1-8/ patient)
  - 40 CRC
  - 12 breast ca
  - 4 gall bladder ca
  - 12 other (lung ca, melanoma..)

  } Refractory to or unsuitable for chemo
- Median volume 75 cc (2 – 3000 cc)
- Median dose 41 Gy (28 – 60 Gy), in 6 fractions

Lee.., Dawson. JCO, April 2009

## PMH Phase I/II Study - Metastases

- Med follow-up 10.8 months, n=68
- Acute Toxicity
  - Fatigue, gr 1 common
  - 3 Gastritis, gr 1/2
- Late Toxicity
  - No liver toxicity
  - 1 intermittent pain (gr 2)
  - 1 rib fracture
  - 1 colitis (gr 2)
  - 1 duodenal bleed (gr 4), in presence of tumor
  - 1 small bowel obstruction (gr 4), in presence of tumor

V. low risk of liver toxicity (95% CI: 0-5.3%)

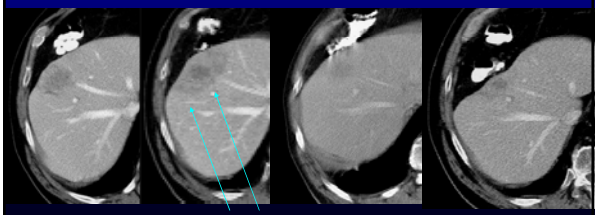
Lee.., Dawson. JCO, April 2009

## Responses

RR 57%, SD 32%, PD 11%

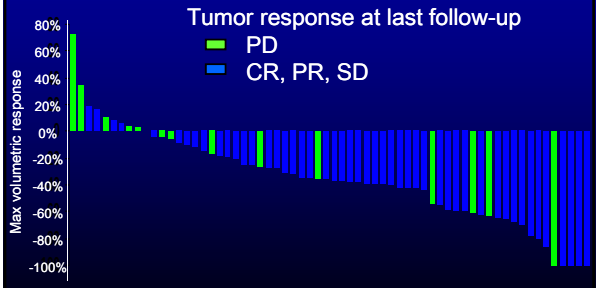
79 y.o. man - rectal cancer liver metastases, bad COPD
Chemo-refractory, 45 Gy/6 #, 'NED' 27 months

Baseline | 1 month | 3 months | 27 months



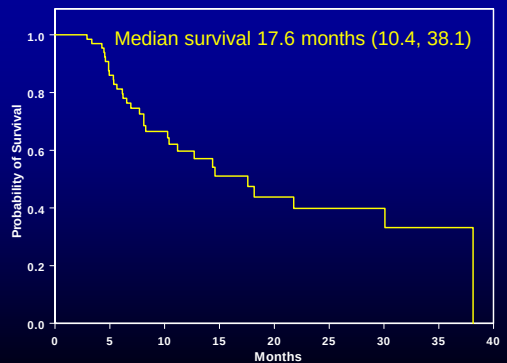
Change due to RT

## PMH Phase I -Tumor control




Lee.., Dawson. JCO, April 2009

## PMH Phase I/II Study - Survival




Lee.., Dawson. JCO, April 2009

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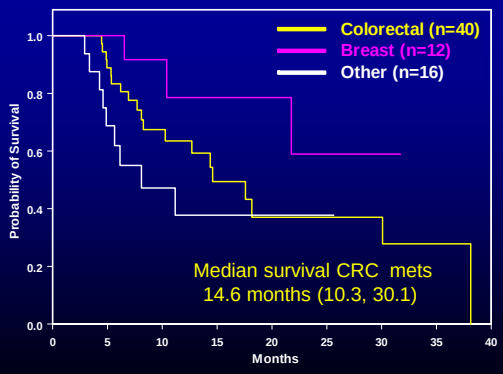


Lee.., Dawson. JCO, April 2009

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## Results: Michigan

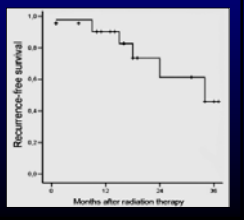
- 82 unresectable HCC or intrahepatic cholangioca
  - Child-Pugh A
  - Median tumor volume 276 cc
  - No portal vein thrombosis
  - Tx with individualized RT 1.5 Gy bid to 90 Gy max, with hepatic arterial 5FUdR

| | HCC | Cholangioca |
|---|---|---|
| – Number | 36 | 46 |
| – Response rate | 58% | 36% |
| – Median survival | 15.2 months | 13.3 months |

FEASIBILITY AND EFFICACY OF HIGH-DOSE THREE-DIMENSIONAL-CONFORMAL RADIOTHERAPY IN CIRRHOTIC PATIENTS WITH SMALL-SIZE HEPATOCELLULAR CARCINOMA NON-ELIGIBLE FOR CURATIVE THERAPIES—MATURE RESULTS OF THE FRENCH PHASE II RTF-1 TRIAL

Françoise Mornex, M.D., Ph.D.,* Nicolas Girard, M.D.,* Christophe Beziat, M.D.,† Abdul Kobai, M.D.,* Mustapha Khoudri,* Christian Trepo, M.D., Ph.D.,† and Philippe Merle, M.D., Ph.D.†

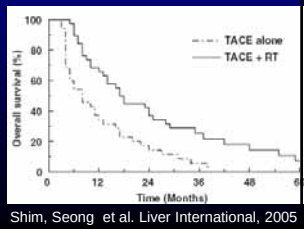
- 25 patients, 1 nodule ≤ 5 cm, 2 nodules ≤ 3 cm
- Radiotherapy; 66 Gy in 2 Gy/fraction
- 60% 2 yr relapse free survival
- Response rate; 92%
  - CR 80%, PR 12%
- Toxicity:
  - 19% Grade 3 in Child A
  - 22% Grade 4 in Child B




## RT & TACE vs TACE - HCC: Korea

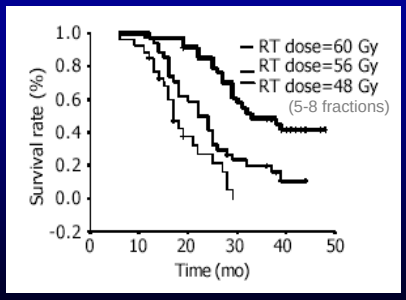
- 73/ 105 HCC incomplete response to TACE
  - 35 TACE repeated
  - 38 received radiotherapy
- Multivariate analysis sign. factors (survival)
  - Tumor size
  - Treatment

| 2 yr survival | RT | no RT |
|---|---|---|
| All | 37% | 14% |
| 5-7 cm | 63% | 42% |
| 8-10 cm | 50% | 0% |




Shim, Seong et al. Liver International, 2005

## China, TACE and RT – Dose Effect (5-10#)

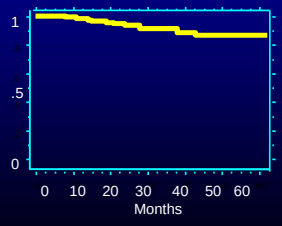



Wu et al. World J Gastroenterol, *2004*

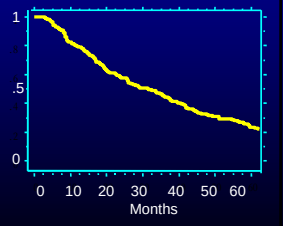
## Protons for HCC: Japan n=162

- Fractionations: 55 – 96.8 GyE / 10-30 fractions
- N=162

5 yr LOCAL CONTROL 87%




5 yr SURVIVAL 24%




Tokuuye, Akine Clin Cancer Res 2005

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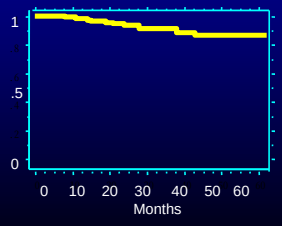
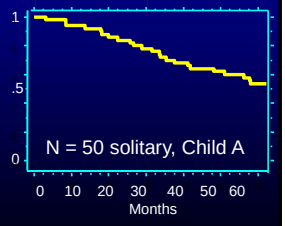



5 yr SURVIVAL 54%




Tokuuye, Akine Clin Cancer Res 2005

## Protons for HCC: Japan n=162

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- N=162

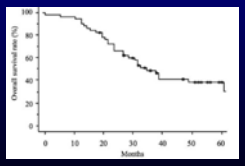
- 5 late toxicities
  - Biliary stenosis 13 months post RT
  - Biloma (2) 29 and 38 months post RT
  - Gastric ulcer 4 months post RT
  - Colon ulcer 6 months post RT

Tokuuye, Akine Clin Cancer Res 2005

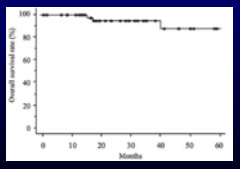
## Protons for HCC: Japan n=51

- Confirmatory prospective studies
- > 2cm from portal hepatis
- 66 GyE in 10#

5 yr survival 39%

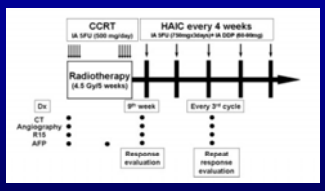


5 yr local control 88%



Fukumitsu, IJROBP, July 1, 2009

## HCC with Portal Vein Thrombosis, Korea




- 40 patients
- RT 45 Gy in 25#, conformal RT
- Concurrent hepatic arterial 5FU wk 1 and 5
- Post RT hepatic arterial 5FU+ Cisplatin
- Median survival 13.1 months

Han, Seong, et al, Cancer 103, Sept 2008

## PMH Phase I Study, n=31 HCC pts, 27–54 Gy in 6#

- Med. Age (range): 66 (41-85)
- HBV: HCV: Etoh: other 13: 12: 4: 2
- Med. AFP (range): 1047 (< 5, 714000)
- Child A5: A6 28:3
- Med. tumor volume 173 cc (9-3090 cc)
- Portal vein/ IVC involvement n=16 (52%)
- Prior treatment: 61 %
  - Resection/ transplant + other 6 (19%)
  - RFA or Etoh ablation only 7 (23%)
  - TACE only 2 (6%)
  - Doxorubicin only 1 (3%)
  - Other combinations 3 (9%)

Tse et al, JCO, 2008

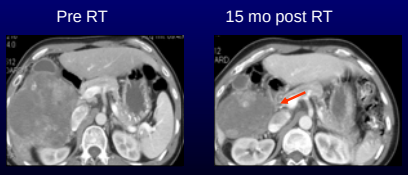
## Phase I Study, HCC Toxicity, n=31

- Grade 3 nausea/vomiting 1
- Grade 1 /2 /3 platelets 21 / 2 / 1
- Radiation Liver Disease, RILD 0
- Grade 3 liver enzymes 8 (6 preexisting)
- Decline in Child score (3 mo) 5
  - Large tumors treated to doses < 36 Gy, 6 #
  - 3 with rapid extensive hepatic progressive HCC
  - 2 with Child A6 function at baseline

Tse et al, JCO, 2008

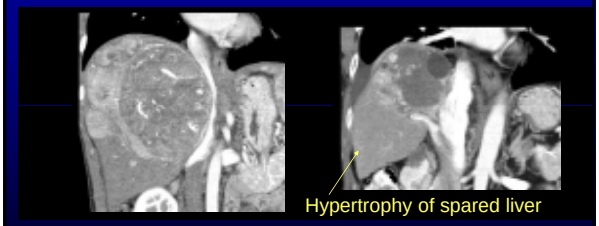
## Late Toxicity

- 1 tumor-duodenal connection: 15 mo post RT (30 Gy in 6#)
  - Detected on imaging, with persistent HCC
  - Ultimate infection and GI bleed leading to death at 18 mo




## Responses

Hepatocellular carcinoma, 33 Gy/ 6 #

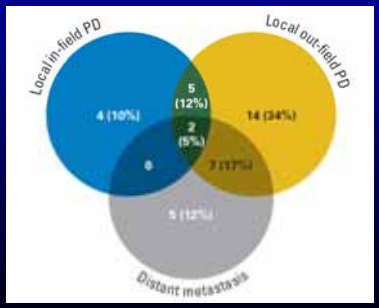



12 mo in-field local control 65% (95% CI: 44, 79%)

SD > PR > CR

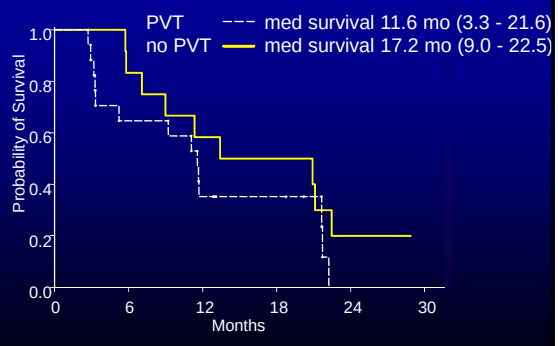
## Patterns of Recurrence

- Majority recur outside irradiated volume




Tse et al, JCO, 2008

## Survival by Portal Vein Thrombosis, PVT




Tse et al, JCO, 2008

## Outline

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients

## Most Suitable Patients

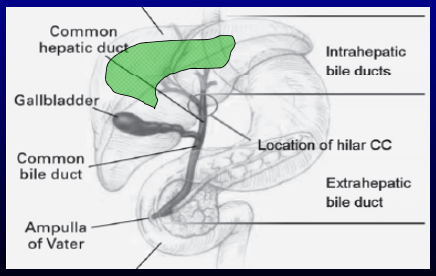
- Liver confined disease
- Not appropriate for other standard local therapies
- > 700 cc uninvolved liver
- No cirrhosis or active hepatitis
- Non-diffuse, focal, < 5 tumors
- < 8 cm diameter metastases
- Breathing motion < 10 mm
- Tumors not adjacent to stomach or small bowel

## More Challenging Patients

- Underlying cirrhosis or Hepatitis
  - Treat viral Hepatitis pre-RT
- < 700 cc uninvolved liver
- > 5 non focal tumors
- > 8 cm diameter tumors
- Breathing motion > 10mm
- Tumors close to stomach or small bowel

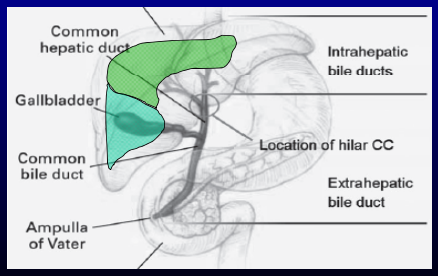
## Location: Lowest Risk to Higher Risk

- Lowest risk: Away from stomach, bowel, caudate lobe, capsule, gall bladder



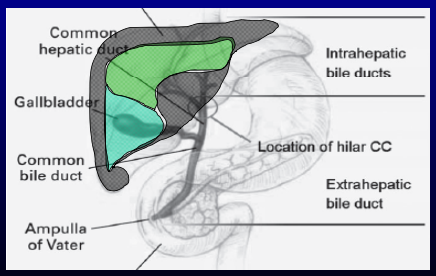

## Location: Lowest Risk to Higher Risk

- Low risk: Away from stomach, bowel, caudate lobe, capsule



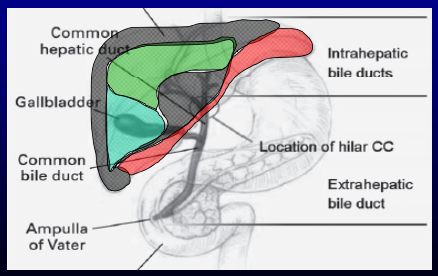

## Location: Lowest Risk to Higher Risk

- Low risk: Away from stomach, bowel




## Location: Lowest Risk to Higher Risk

- Risk of stomach and bowel toxicity: Near stomach and small bowel



## Ongoing External RT Studies

- RTOG phase I mets: 40-50 Gy in 10# (PI: Katz)
- Ph II: RT in CRC metastases (PI: Dawson)
- Ph II: RT in HCC (PI: Dawson)
- Ph I: RT + sorafenib in HCC (PI: Dawson)
- Ph I: RT + sorafenib in mets (PI: Dawson)
- Randomized Ph II : sorafenib +/- RT for HCC (PI: Dawson, RTOG)
- Ph III : SBRT (12 – 16Gy x 3) vs RFA for unresectable CRC liver mets < 4cm (PI: Hoyer- Denmark, Mendez- Netherlands)

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## $^{90}$Y Radioembolization Devices

- TheraSphere® 
- MDS Nordion, Canada
- Glass
- Yttrium-90
- Size = 25 microns
- # spheres/tx = 1.2-8 million
- FDA approved for HCC
- European approval for liver cancer

- SIR-Spheres® 
- Sirtex Medical, Australia
- Resin
- Yttrium-90
- Size = 35 microns
- # spheres/tx = 0-30 million
- FDA approved for colon liver metastases
- European approval for liver cancer

Physical half life 64 hr
Penetration range: Ave ≈ 2.5 mm, max 10 mm

## Workup algorithm

- Review of case-cirrhosis, portal HTN, tumour burden
- Angiographic evaluation-shunting
  - Tc99m-MAA
  - coil embolization of vessels
- Dose calculation based on target liver volume (lobe/segment)
  - 80-150 Gy, wide range allows for flexibility in treatment
  - Typical treatment range is 100–120 Gy
- 2 treatments using lobar/segmental approach

Angiographic Considerations in Patients Undergoing Liver-directed Therapy

David M. Liu, MD, Riad Salem, MD, MBA, James T. Bui, MD, Angi Courtney, PA-C, Omar Barakat, MD, Ziad Sergie, MD, Basel Atassi, MD, Karen Barrett, RN, Patricia Gowland, RN, Beth Oman, RN, Robert J. Lewandowski, MD, Vanessa L. Gates, MS, Kenneth G. Thurston, MA, and Ching-yee O. Wong, MD, PhD

Radioembolization with $^{90}$Y Microspheres: Angiographic and Technical Considerations

Robert J. Lewandowski · Kent T. Sato · Bassel Atassi · Robert K. Ryu · Albert A. Nemcek Jr. · Laura Kulik · Jean-Francois Geschwind · Ravi Murthy · William Billing · David Liu · Lourens Bester · Jose Ignacio Bilbao · Andrew S. Kennedy · Reed A. Omary · Riad Salem

Technical Aspects of Radioembolization with $^{90}$Y Microspheres

Riad Salem, MD, MBA,[1-3] Robert J. Lewandowski, MD,[1] Kent T. Sato, MD,[1] Bassel Atassi, MD,[1] Robert K. Ryu, MD,[1] Saad Ibrahim, MD,[1] Albert A. Nemcek, Jr, MD,[1] Reed A. Omary, MD, MS,[1] David C. Madoff, MD,[1] and Ravi Murthy, MD[1]

Liu et al JVIR 2005 Lewandowski et al CVIR 2007 Salem et al TVIR 2007

## Potential Complications and Solutions

1) Gastrointestinal
- Gastritis ===> Proton pump inhibitors
- Ulceration ===> lobar approach (distal to collaterals)

2) Abdominal Pain Prevention
- Burning ===> prophylactic embolization/identification of collaterals

3) Fatigue ===> 5-7 day steroid dose pack

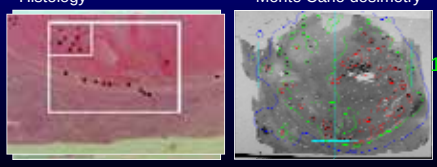
4) Dose Selection
- Wide range ===> segmental infusion

## Hepatic Arterial Yttrium-90 Microspheres

- Liver sparing via
  - Hepatic arterial delivery
  - Subsegmental delivery versus whole liver
  - Rapid fall off in dose (ave range ≈ 2.5 mm)

Histology | Monte Carlo dosimetry

Y90 spheres around and in HCC



100 Gy

Kennedy, et al. IJROBP 60(5), 2004

## Radiologic–Pathologic Correlation of Hepatocellular Carcinoma Treated with Internal Radiation Using Yttrium-90 Microspheres

- 35 patients with a total of 38 lesions who underwent liver explantation after Y-90
- 90% of lesions < 3cm complete necrosis
- Less chance of complete necrosis with increasing tumor size
  - Increased chance of 'cold spot' with larger tumors

Riaz et al Hepatology 2009

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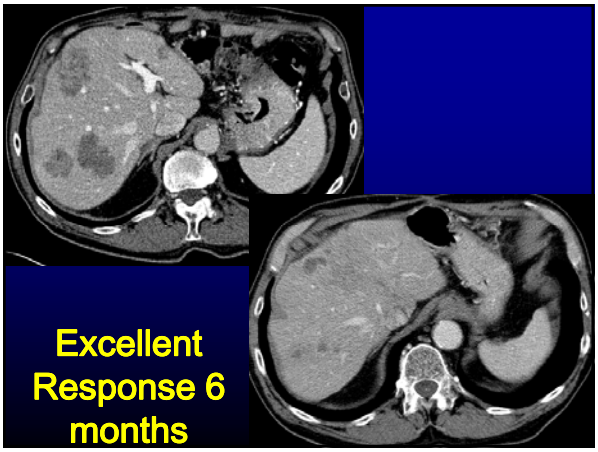
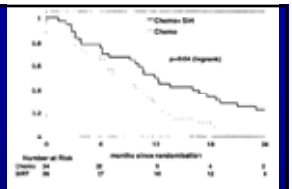


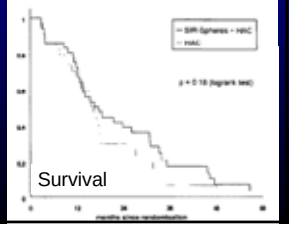
Excellent Response 6 months

## Randomised trial of SIR-Spheres plus hepatic arterial FUDR vs. FUDR alone for patients with CRC liver metastases

- 74 CRC patients randomised to Y90 + FUDR vs FUDR
- Response: 50 % vs 24%
- TTP: 12 vs 7.6 months



Time to Progression



Survival

Gray et al, Ann Oncol 2001

## Van Hazel Randomized Phase II

- 1st line liver metastases from CRC
- 5FU/leucovorin (n=10) +/- SIRT (n=11)
- Best response: 8 PR 3 SD vs 0 PR 6 SD 4 PD
- Time to progression: 18.6 mo vs 3,6 mo p<0.0005
- Med survival: 29.4 mo vs 12.8 mo p=0.02

Van Hazel et al (Australia), J Surg Oncol 88:78-85,2004

## Belgium Randomized Phase III

- Chemo-refractory CRC
- 5FU infusion +/- Y90
- 44 eligible patients randomized
- Med fu 24.9 mo
- Med TTP improved: 2.1 mos to 4.6 mos (p=0.03)
- Med TTLP improved: 2.1 mos to 5.1 mos (p=0.003)
- Increased toxicity in 5FU alone arm

Van den Engel, ASCO 2009, #4096

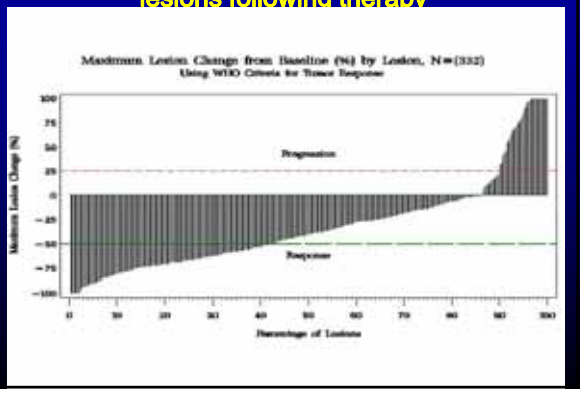
## Unresectable Chemorefractory Liver Metastases: Radioembolization with $^{90}Y$ Microspheres—Safety, Efficacy, and Survival[1]

- 137 patients with chemorefractory liver metastases
- WHO response rate: 42.8% (2.1% CR, 40.7 PR)
- Biologic tumor response rate: 87% (any decrease in tumor size)

- Median survival:
  - colorectal: 15.2 mo
  - neuroendocrine: 25.9 mo
  - non-colorectal, non-neuroendocrine: 6.9 mo

Sato et al Radiology 2008

## Change from baseline in cross product of lesions following therapy




## Survival Analysis(Cont..)

| | N | Median in days | 1-Yr Survival (%) | 2-Yr Survival (%) | P-value |
|---|---|---|---|---|---|
| Angiographic Vascularity | | | | | 0.9546 |
| Hyper | 108 | 300 | 48.5 | 25.9 | |
| Hypo | 29 | 261 | 47.9 | 32.8 | |
| | | | | | |
| CT Vascularity | | | | | 0.6712 |
| Hyper | 24 | 306 | 47.6 | 30.5 | |
| Hypo | 113 | 284 | 48.3 | 31.1 | |
| | | | | | |
| >4 Lesions | | | | | 0.0126 |
| Yes | 91 | 234 | 37.4 | 28.4 | |
| No | 46 | 632 | 68.6 | 38.1 | |
| | | | | | |
| Tumor Burden | | | | | 0.0005 |
| 0-25% | 109 | 506 | 54.6 | 35.8 | |
| 26-50% | 21 | 181 | 33.2 | 22.1 | |
| 51-75% | 7 | 158 | 0 | 0 | |
| > 76% | 0 | - | - | - | |

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## Hepatic Arterial Iodine-131 Lipiodol

- RCT in resected HCC
  - N=74
  - Hepatic arterial I-131 Lipiodol versus no further therapy
  - 3 yr DFS improved from 36% to 74%, p=0.04
  - 3 yr survival improved from 46% to 86%, p=0.04

- Underpowered

* Lau, Lancet 353, p797, 1999

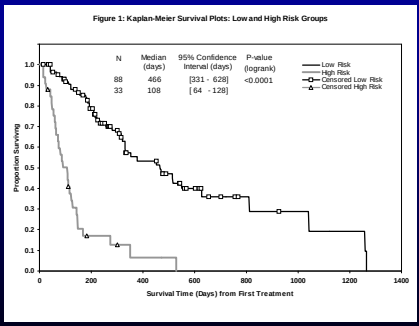
## Hepatic Arterial Yttrium-90 - HCC

| Study | No of HCC Patients | Survival |
|---|---|---|
| Dancey et al 2000 | 20 | Median = 54 weeks |
| Carr 2004 | 65 | Okuda I (n=42) Median = 649 d<br>Okuda II (n=23) Median = 302 d |
| Geschwind et al 2004 | 80 | Okuda I (n=54) Median = 628 d<br>Okuda II (n=26) Median = 384 d<br>CLIP 0 (n=26) Median = 812 d<br>CLIP 1-2 (n=41) Median = 452 d<br>CLIP > 2 (n=13) Median = 216 d |
| Liu et al 2004 | 11 | Okuda II (n =7) Median = 11 mo<br>Okuda III (n=4) Median = 7 mo |
| Salem et al 2004 | 43 (86 tumors) | Okuda I (n=21) Median = 617 d<br>Okuda II (n=22) Median= 315 d |

## Goin et al
## Treatment of Hepatocellular Carcinoma with Intrahepatic Y90 Microspheres: A Risk Stratification Analysis
*Journal of Vascular & Interventional Radiology 2005*

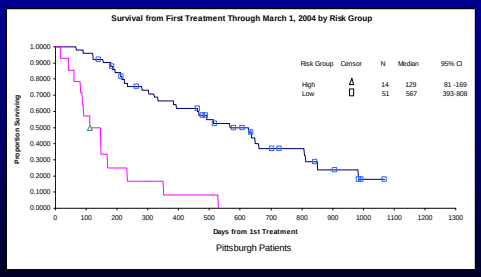
- 121 HCC patients, from 5 institutions
- Identified high-risk versus low-risk patients
- 5 high risk factors identified
  - Infiltrative tumor
  - AST/ALT > 5 ULN
  - Tumor burden > 50% and albumin < 3.0 g/dl
  - Bilirubin > 2 mg/dl
  - Bulk disease
- Conclusions:
  - Risk variables critical in identifying patients for Y90
  - Low risk survival: 15.5 mos
  - High risk survival: 3.6 mos

## Survival of Patients in Low and High Risk Groups

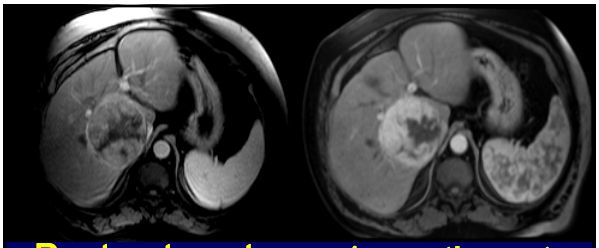



*Goin et al, Risk Stratification Analysis, JVIR, 2005

## University of Pittsburgh: Patient Survival for High and Low Risk Groups (65 patients)*



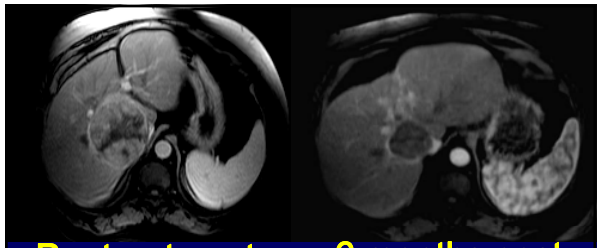

*Goin et al, Risk Stratification Analysis, JVIR, 2005



Pre treatment AFP → 2200

1 month post treatment AFP →130

Courtesy of Riad Salem, Chicago

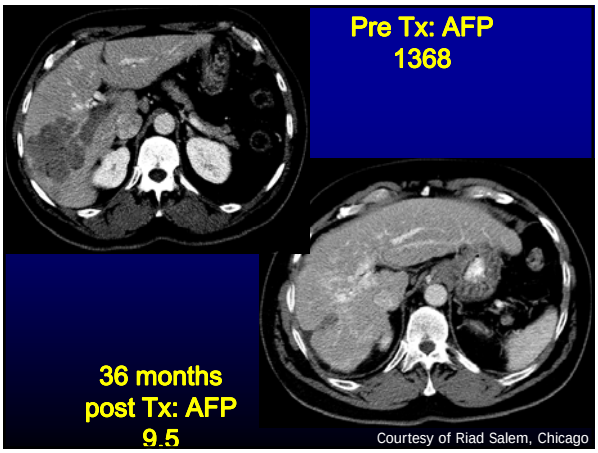


Pre treatment AFP → 2200

6 months post treatment AFP → 4.5

Courtesy of Riad Salem, Chicago

# PORTAL VEIN THROMBOSIS




## Safety and Efficacy of $^{90}$Y Radiotherapy for Hepatocellular Carcinoma With and Without Portal Vein Thrombosis

Laura M. Kulik,[1] Brian I. Carr,[2] Mary F. Mulcahy,[3] Robert J. Lewandowski,[4] Bassel Atassi,[4] Robert K. Ryu,[4] Kent T. Sato,[4] Al Benson III,[5] Albert A. Nemcek, Jr.,[4] Vanessa L. Gates,[4] Michael Abecassis,[5] Reed A. Omary,[4] and Riad Salem[3,4]

- 108 HCC patients
  - 37 with PVT
  - 71 without PVT
  - Analyzed toxicities based on:
    - Child Pugh in cirrhotics
    - Dose
    - Location of PVT
  - Assessed overall survival

Kulik et al Hepatology Jan 2008

## Safety and Efficacy of $^{90}$Y Radiotherapy for Hepatocellular Carcinoma With and Without Portal Vein Thrombosis

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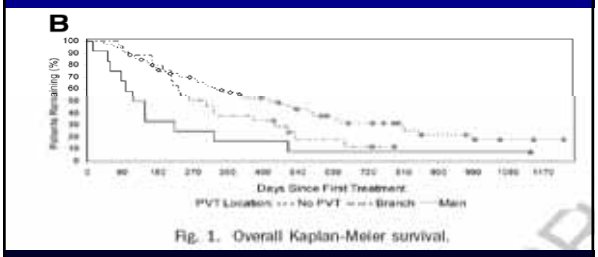


Fig. 1. Overall Kaplan-Meier survival.

Kulik et al Hepatology Jan 2008

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  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
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  - Most suitable patients

## Patient Selection Criteria

- Non-Infiltrative disease
- AST/ALT < 5 x ULN
- Tumor Volume ≤ 50%
- Albumin > 3 g/dL
- Bilirubin ≤ 2 mg/dL
- Good performance status
- Appropriate vascular anatomy
  - <20-30% hepatopulmonary shunting
  - Able to embolize aberrant vessels

Goin et al, Factors Associated with Liver Toxicities, JVIR, 2005

## Conclusions

- High dose conformal RT and internal RT can be delivered safely to unresectable liver metastases and hepatocellular carcinoma
- Sustained local control is possible
- Optimal integration of RT with other therapies unknown
- Quality assurance and education important for both external and internal RT
- Multi-disciplinary team required
- Strong rationale and need for randomized trials


## Acknowledgements

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Cynthia Eccles
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Gina Lockwood

Jennifer Knox
Morris Sherman

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