Hepatocellular Carcinoma

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MS IV
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Overview

Hepatocellular Carcinoma Overview

Summary of Treatment Options

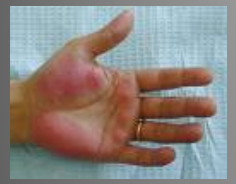
Radiation Therapy and HCC

Epidemiology

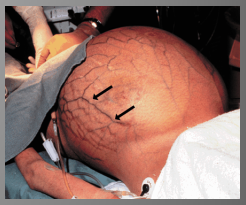
- 6th most common cancer worldwide
- >600,000 deaths worldwide per year
    - >17,000 deaths in USA
- Highest incidences in developing countries
    - Africa, Asia, Melanesia
    - High incidence in Japan
- Male/Female Ratio: ≈2.6

Risk Factors

- Chronic Hepatitis B/C: relative risk ≈ 100
- Chemical Injury
  - ethanol, nitrites, hydrocarbons, pesticides, etc..
- Environmental Toxins
  - aflatoxin, betel nut chewing, contaminated drinking water
- Hereditary Liver Disease
  - Hemochromatosis, Wilsons Disease, Type 1 Glycogen Storage Disease
- Cirrhosis – with any of the above causes
  - With any of the above causing repetitive inflammation and scarring



Clinical Presentation



- Early in disease course patients can be asymptomatic
- Symptoms usually due to chronic hepatitis or cirrhosis
    - Fatigue, ascites, jaundice, dilated abd. veins, palmar erythema, gynecomastia, etc.
- Tumor induced symptoms:
    - Hepatomegaly, RUQ pain, obstructive jaundice, splenomegaly

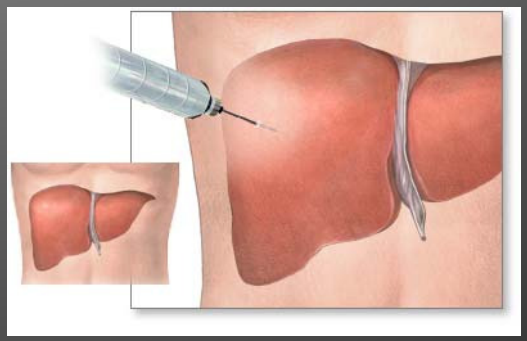
Workup

Imaging:

Ultrasound,
CT

Labs:

CBC, LFT's, chemistries, coag panel, Hep B/C panel, alpha-feto protein (10-15% false negative rate)



Biopsy may not be required

Based off of history and clinical presentation

Staging

Primary Tumor
(T) TX Primary tumor cannot be assessed T0 No evidence of primary tumor
T1 Solitary tumor without vascular invasion
T2 Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
T3 Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4 Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

Regional Lymph Nodes
(N) NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis
(M) MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage I T1 N0 M0
Stage II T2 N0 M0
Stage IIIA T3 N0 M0 IIIB T4 N0 M0 IIIC Tx N1 M0
Stage IV Any T Any N M1

5 yr Survival by Stage

Stage I 50-60%
Stage II 30-40%
Stage III 10-20%
Stage IV <10%
Unresectable (unresponsive) <10%

Treatment Options

Operable	Nonoperable
Partial Hepatectomy	Radiofrequency Ablation
Liver Transplant	Percutaneous Ethanol Ablation
	Transarterial Chemoembolization
	Cryoablation
	Systemic Chemotherapy
	Radiation Therapy
	Radioembolization

Partial Hepatectomy

- Optimal treatment when possible
  - Surgery still considered mainstay therapy
- Patients tend to be highly selected
  - Patient frequently have severe liver disease → surgically suboptimal

Optimal Criteria
Solitary tumor < 5 cm
No vascular invasion
No portal hypertension
Well-preserved hepatic function (Child-Pugh Class A

Stage 1-2	
5 yr OS	Ranges ≈ 40% - 90%
Long term recurrence free	≈40%

Liver Transplant

- Frequently the only surgical option due to liver dysfunction
- Very good outcomes
- Long wait times, unpredictabile
    - MELD scores used for allocation in USA

Optimal Criteria
Solitary tumor < 5 cm
Up to three nodules <3 cm
No vascular invasion
No regional nodal or distant metasteses

Stage 1-2	
3 yr OS	≈ 75%

Percutaneous Ablation

- Injection of ethanol or acetic acid → cellular dehydration → tumor necrosis and fibrosis
- Replaced in popularity by RFA

Optimal Criteria
Early stage HCC
Not resectable
Solitary tumors <3cm

Child-Pugh Class A, <5cm	
Complete Ablation	70-75%
5 yr OS	47%

Radiofrequency Ablation

- Electrode insertion into lesion → high frequency alternating current → ions attempt to follow current resulting in high frictional energy → cell death
- Less side effects than PEI with better outcomes
- Similar results to surgery in potentially resectable patients

Optimal Criteria
Child-Pugh Class A/B
Solitary tumors <4cm

Child-Pugh Class A/B	
3 yr OS	78-87%

Radiofrequency Ablation

Transarterial Chemoembolization

- Intraarterial embolization with lipoidol and chemotherapy (doxorubicin or cisplatin)
- Standard palliative treatment for patients with unresectable HCC
- 4/6 randomized trials failed to show survival benefit over conservative management

Indications
Large unresectable HCC
Prior to resection or RFA
Palliative purposes

Cryoablation

- Intraoperative cryoprobe tumor insertion with alternating freeze/thaw cycles
- Largely replaced by RFA
- High complication rates

Optimal Criteria
Tumors <5cm

Early Stage	
3 yr OS	52-77%

Radiation

- Radiosensitive cancer (at high doses), but in a very radiosensitive organ; toxicity easily achieved
- Complications of liver failure can make treatment planning difficult
- Whole liver - palliative
- Partial liver – definitive treatment

Indications
Large unresectable HCC
Symptomatic portal vein thrombosis
Symptomatic jaundice
Part of combined modality treatment

RT – Historical Perspective

- Palliative Use
  - Whole liver radiation
    - Borgelt (IJROBP, 1983)
      - Whole liver RT can relieve symptoms
      - Ascites, anorexia, pain, nausea, vomiting, fever, etc.
    - Russell (IJROBP, 1993)
      - 21 Gy standard dose
      - Dose escalation 27Gy →30Gy →33Gy
      - No injury at 27Gy and 30Gy → toxicities started developing at 33 Gy

RT – Historical Perspective

- U. of Michigan – Dawson, 2002
  - Use of conformality for partial liver treatments
    - Response rates 50-70%
  - Approach is to prescribe dose that gives 10% risk of RILD based on NTCP model
    - RILD – radiation induced liver disease
    - NTCP – normal tissue complication probability

$$NTCP = \phi(t) = 1 \Big/ \sqrt{2\pi} \int_{-\infty}^{t} e^{-x^2/2} dx$$

  - Liver Tolerance Histograms
    - No RILD (Radiation Induced Liver Disease) with mean liver dose <31 Gy
    - RILD depends on volume of liver receiving radiation

RT - Constraints

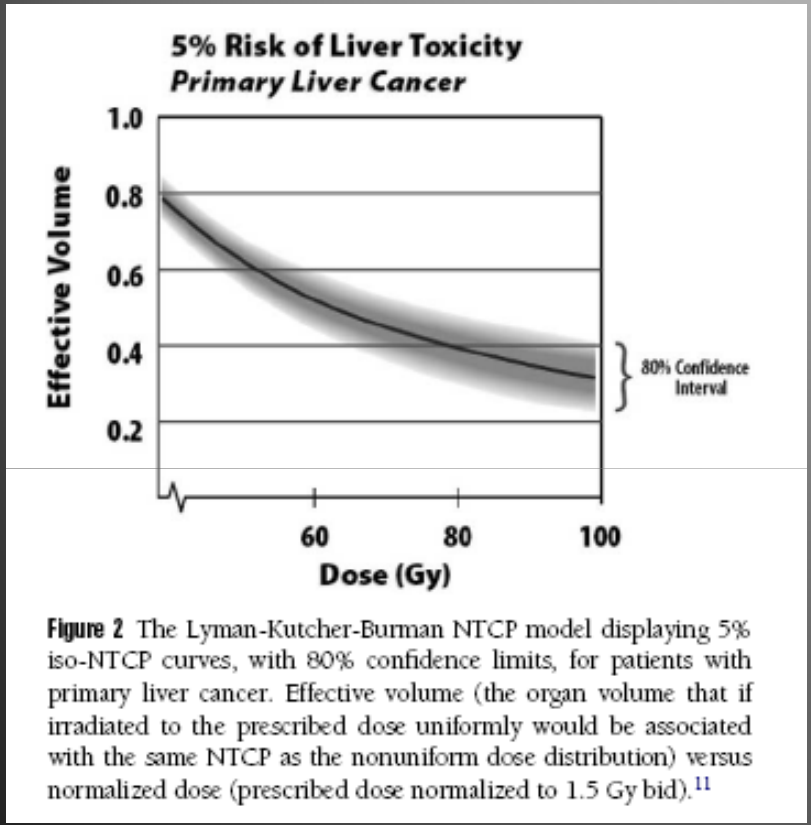


Figure 2 The Lyman-Kutcher-Burman NTCP model displaying 5% iso-NTCP curves, with 80% confidence limits, for patients with primary liver cancer. Effective volume (the organ volume that if irradiated to the prescribed dose uniformly would be associated with the same NTCP as the nonuniform dose distribution) versus normalized dose (prescribed dose normalized to 1.5 Gy bid).[11]

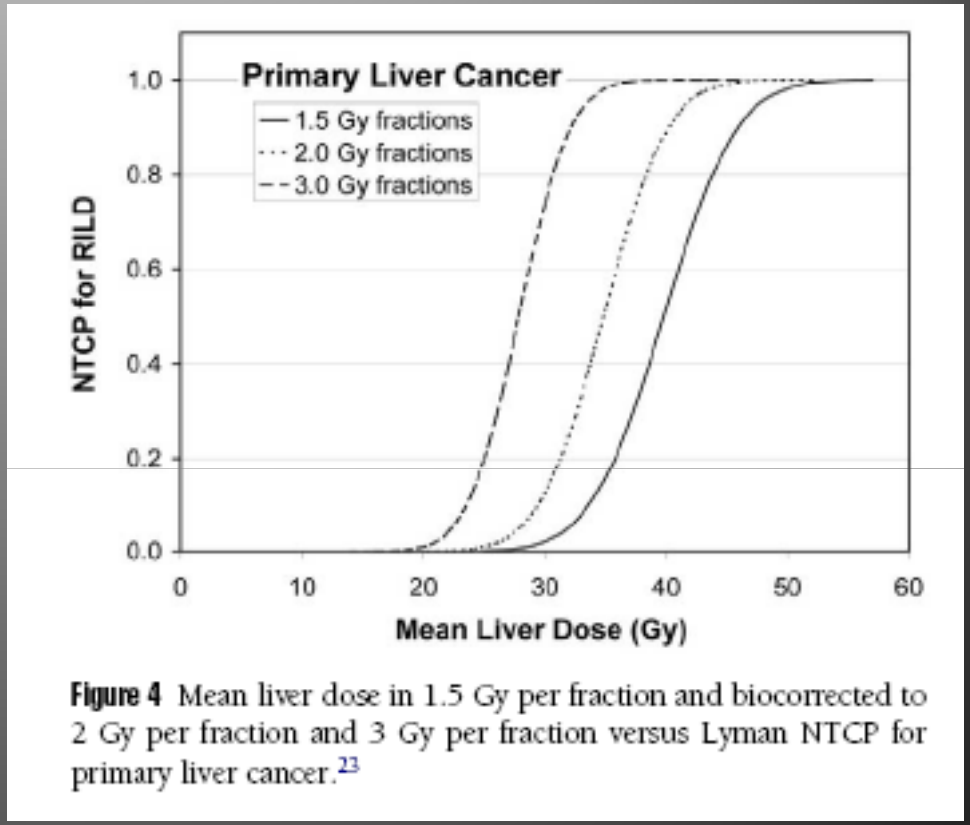


Figure 4 Mean liver dose in 1.5 Gy per fraction and biocorrected to 2 Gy per fraction and 3 Gy per fraction versus Lyman NTCP for primary liver cancer.[23]

*Dawson, Seminars in Rad Onc, 2005

Whole liver
TD 5/5: 30Gy/15 fx
TD 50/5: 42Gy/21 fx
2/3 Liver TD5/5: 50.4Gy/28fx
1/3 Liver TD5/5: 68.4Gy/38fx

RT – 3D Conformal

TABLE 1. *Clinical outcomes after photon RT for hepatocellular carcinoma*

Study	n	RT	Added therapy	Objective response rate	Grade ≥3 toxicity rate	In situ recurrence rate	Multifocal recurrence rate	Median survival (mo)	Survival rate
Robertson et al., 1993[8]	11	48–72 Gy	HAI FUDR	100%	16%	–	–	–	–
Yasuda et al., 1999[50]	44	36–70 Gy	TAE/PEI	–	–	–			81% (3 y)
Dawson et al., 2000[73]	27	30–90 Gy	HAI FUDR	45%	10%	–	–	11	–
Park et al., 2002[74]; Seong et al., 2003[75]	158	40–60 Gy	TACE (107)	67%	–	7%	34%	10	42% (1 y) 20% (2 y)
Chia-Hsien Cheng et al., 2001[52]	26	41–53 Gy	TACE (17)	–	–	11%, 12%	33%, 59%	–	57% (2 y)
Guo et al., 2003[76]	76	30–50 Gy	TACE	48%	–	13%	–	19	64% (1 y) 19% (5 y)
Li et al., 2003[77]	45	50.4 Gy	TACE	91%	27%	27%	–	24	69% (1 y) 23% (3 y)
Cheng et al., 2004[14]	89	36–66 Gy	TACE (74)	–	–	–	–	–	–
Liu et al., 2004[78]	44	40–60 Gy	-	61%	0%	0%	43%	15	61% (1 y) 40% (2 y)
Zeng et al., 2004[79]	54	40–60 Gy*	TACE	76%	–	0%	65%	20	72% (1 y) 6% (5 y)
Wu et al., 2004[80]	94	48–60 Gy	TACE	91%	–	3%	–	25	94% (1 y) 26% (3 y)
Ben-Josef et al., 2005[9]	35	40–90 Gy	HAI FUDR	56%	30%	0%	64%	15	
Park et al., 2005[81]	59	30–55 Gy		66%	0%	24%	–	10	27% (2 y)
Zhou et al., 2006[82]	50	30–54 Gy*	TACE	18%	6%	62%	60%	17	60% (1 y) 28% (3 y)
Mornex et al., 2006[33]	27	66 Gy	–	92 %	41%	22%	41%	–	–

RT, radiotherapy; HAI, hepatic arterial infusion; FUDR, floxuridine; TAE, transarterial embolization; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.
* Hypofractionated regimens used.

*Krishnan, Annals of Surgical Oncolgy, 2008

RT – 3D Conformal

- French RTF1 prospective phase 2 trial (IJROBP, 2006)
  - Investigated high-dose RT for unresectable cirrhotic patients

Methods
25 Pts, Child-Pugh A/B, small HCC
Ineligible for curative therapies
66 Gy in 2 Gy Fx
Results
1 yr Local Control: 78% (92% tumor response)
Grade 4 toxicities in 22% of Child-Pugh B pts only, (already had Grade 3)

RT – 3D Conformal

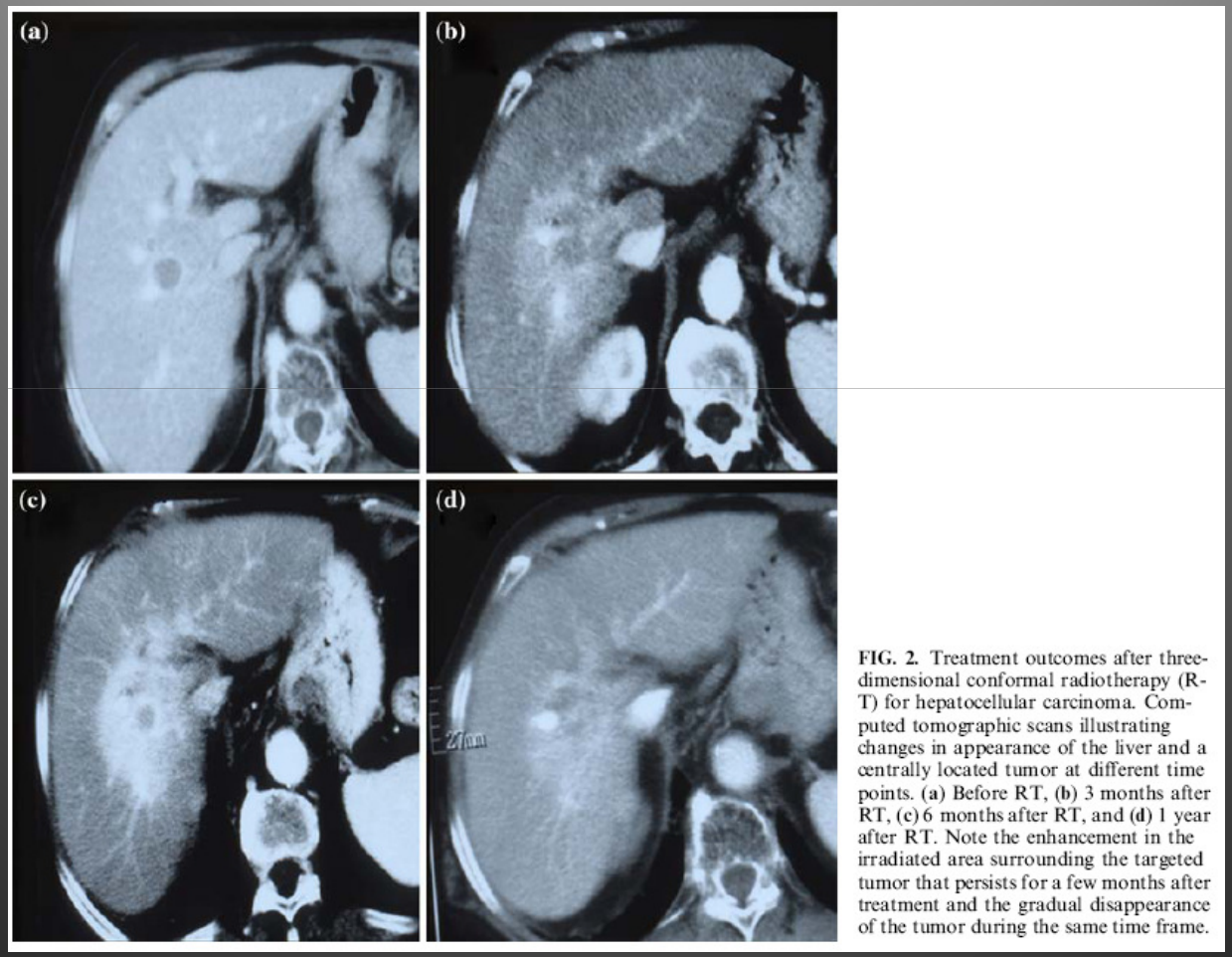


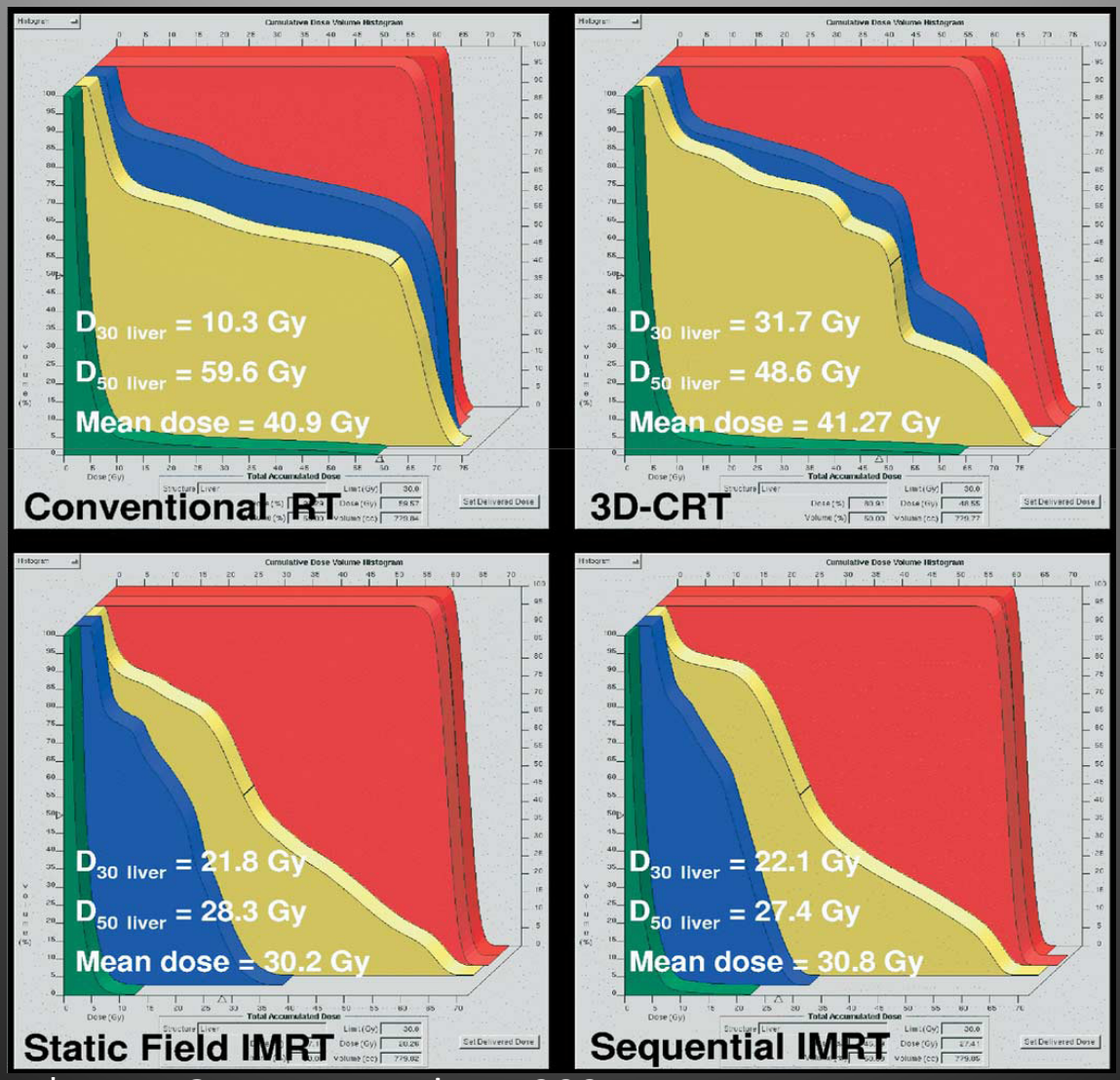
FIG. 2. Treatment outcomes after three-dimensional conformal radiotherapy (R-T) for hepatocellular carcinoma. Computed tomographic scans illustrating changes in appearance of the liver and a centrally located tumor at different time points. (a) Before RT, (b) 3 months after RT, (c) 6 months after RT, and (d) 1 year after RT. Note the enhancement in the irradiated area surrounding the targeted tumor that persists for a few months after treatment and the gradual disappearance of the tumor during the same time frame.

*Krishnan, Annals of Surgical Oncology, 2008

RT - IMRT

- Ongoing area of research
  - IMRT improves conformality but at the cost of low dose to normal tissue
  - Conflicting results indicate increased mean liver dose, but decreased complication predictions based off of NTCP
  - No prospective comparisons published to establish efficacy

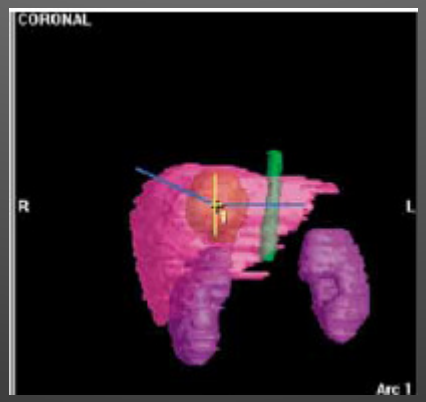
RT - IMRT



* Fuss, Gastroenterology, 2004

RT – Hypofractionated/SBRT

- Hypofractionation Responses
  - Local control ranges 73-93% (Mendez, 2006)
- Ongoing area of research
  - Local experiments with hypofractionated courses



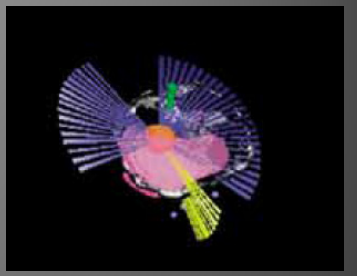
*Cardenes, IJROBP, 2005

RT – Hypofractionated/SBRT

- Dawson (IJROBP, 2007)
  - Phase 1 study of SBRT for unresectable HCC
  - No RILD observed, minimal toxicity incidence
  - Concluded SBRT safe treatment

Methods
31 Pts, Child-Pugh A
25-57 Gy in 6 Fractions
Utilized NTCP model for dose prescription
Results
9 month local control: 78%
Median Survival: 11 months

RT – Hypofractionated/SBRT



- Cardenes (IJROBP, 2008)
  - Dose escalation for primary HCC
  - Concurred SBRT safe treatment
    - 2 pts developed Grade 3 toxicity with high doses
      - » scores of C-P > 8
    - No significant toxicities with dose adjustments

Methods
16 Pts, Child-Pugh A,B
48 Gy (3 Fx) for class A
40 Gy (5 Fx) for C-P >8

RT – Hypofractionated/SBRT

- Costantino (IJROBP, 2003)
  - SBRT in smaller fraction sizes

Methods
54 Pts, Child-Pugh A,B
30 Gy mean dose
4-9 Gy, 3-12 Fx
Results
31 month local control: 94%
Median Survival: 6.4 months

RT – SBRT

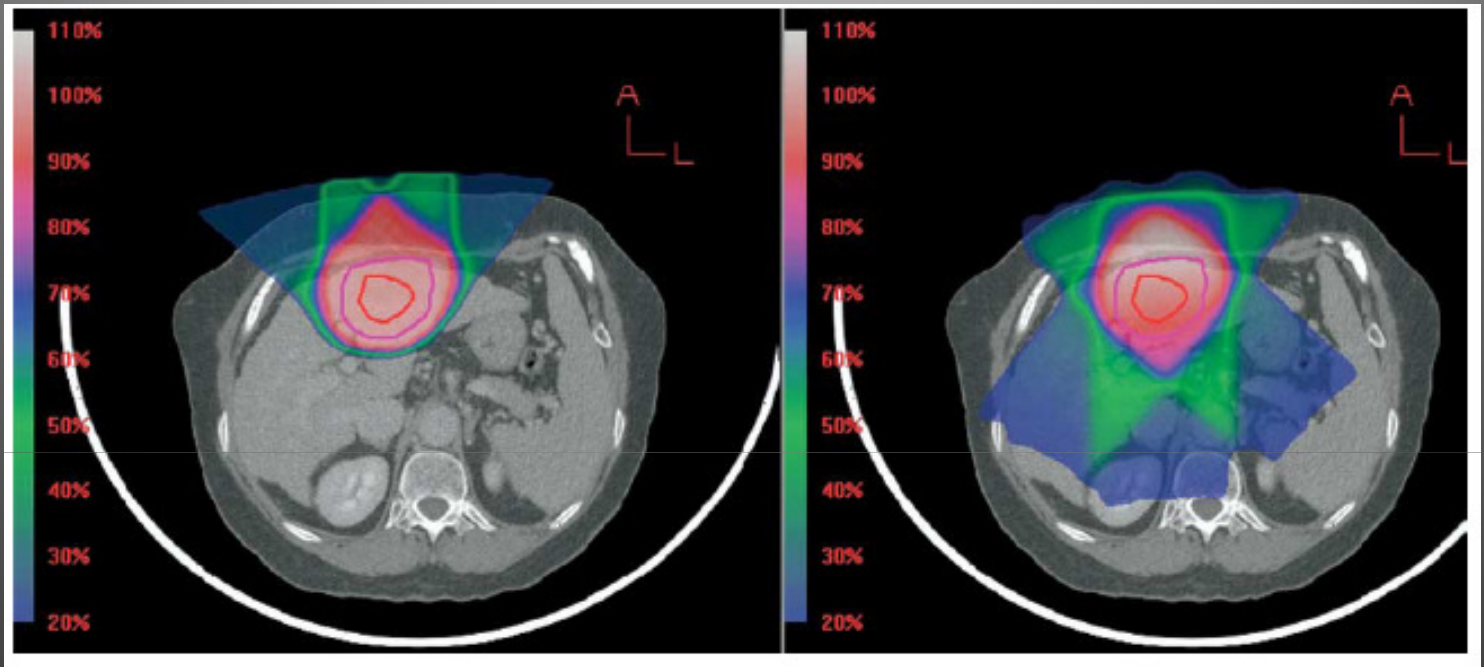
- Studies for Liver Metastases
  - Wulf 2001 – 24 Lesions
    - 18 month Local Control: 61%
  - Herfarth, Debus 2005 – 70 pts, (22 Gy, single Fx)
    - 18 month Local Control: 66%
  - University of Colorado – 2006, 28 Lesions (60 Gy, 3 Fx)
    - 18 month Local Control: 93%
    - Ongoing study

RT – SBRT vs RFA

- European Liver Tumor Group
  - Randomized phase III trial comparing RFA vs SBRT

	SBRT	RFA
Local Control (18 months)	61-93%	70-96%

RT – Charged Particles



*Bush, Gastroenterology, 2004

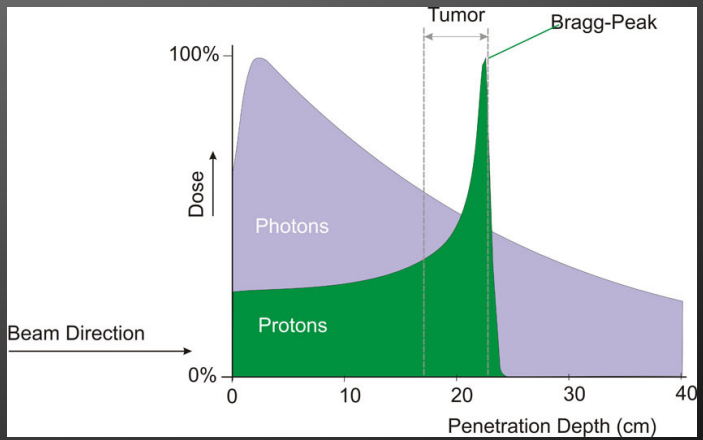


*Image borrowed from Varian Technologies

RT – Charged Particles

- Japan trials with protons (Chiba, Clinical Cancer Research, 2005)
  - Retrospective review over 15 years

Methods
162 pts, mostly Child-Pugh A/B
With/without TACE, PEI
72 Gy in 16 Fx
Results
5 yr local control: 87%
5 yr OS: 23.5%
New HCC lesion: 85%

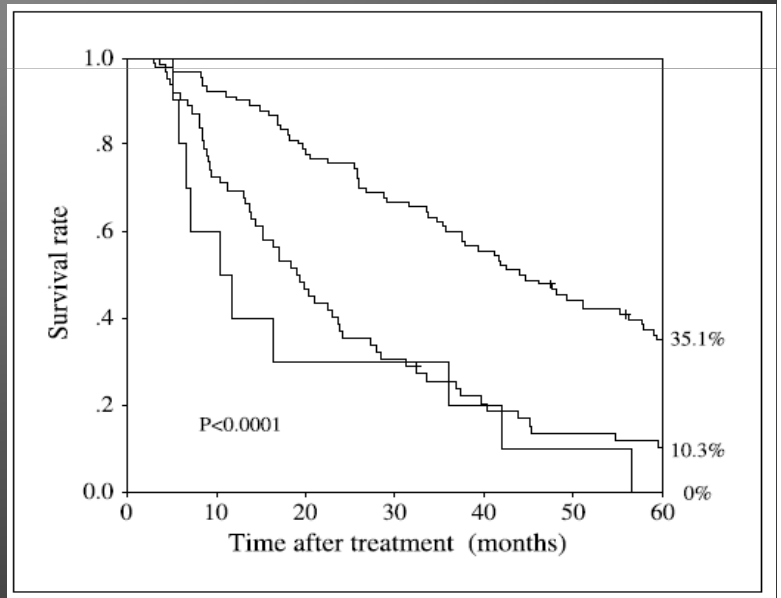


Fig. 3. Survival for the patients according to the degree of hepatic dysfunction. For patients with chronic hepatitis and Child-Pugh class A-C cirrhosis, the 5-year survival rates were 35.1%, 10.3%, and 0%, respectively.

RT – Charged Particles

- Loma Linda Phase 2 trial (Bush, 2004)
  - Preliminary results of proton treatments

Methods
34 Pts, Child-Pugh A/B
63 Gy in 15 Fx
Results
2 yr Local Control: 75%
2 yr OS: 55%
New HCC lesion: 35%

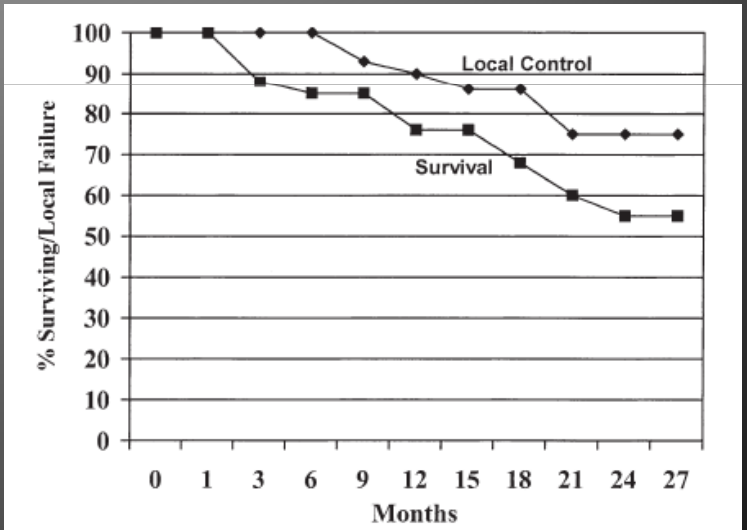


Figure 4. Local tumor control and overall survival.

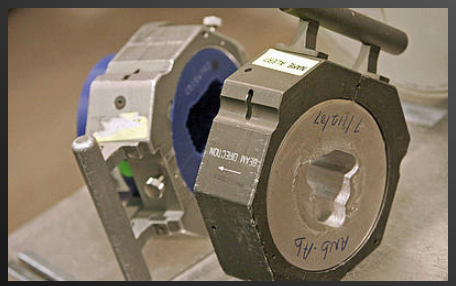
RT- Charged Particles

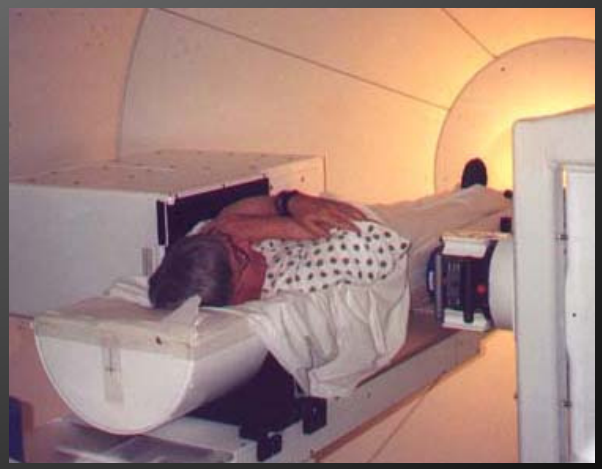
- Ongoing research for re-irradiation in Japan and at Loma Linda
    - Japanese reviews of 27 Child-Pugh A pts with re-irradiation with decreased doses indicate efficacy and safety
- Japanese trials with carbon – ion RT

Research Experience

- 78 Pts treated with proton therapy
  - Child – Pugh A/B
  - 63 Gy in 15 Fx

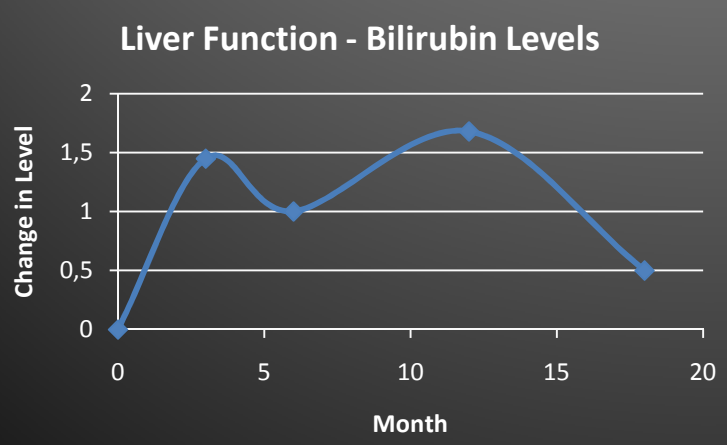
- Premilinary results from ≈ 3/4 pts
  - 5 yr OS : 24%
  - 5yr Local Control: 71%

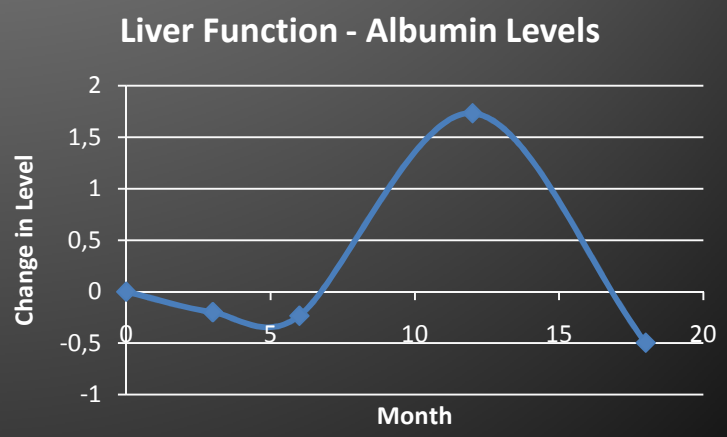




Research Experience

- Subgroup Analysis
  - Margin reductions: Globally, locally
    - » No difference in local control rates
  - Decreased doses to 90% volumes
    - » No difference in local control rates
- Liver Function





Questions?