Educational Workshop

Liver

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2013 PTCOG EW, Essen

Liver : Topics for today

- Anatomy
- Tolerance to RT
- Epidemiology
- Risk factors of liver cancer
- Pathology
- Treatment options
- Particle therapy

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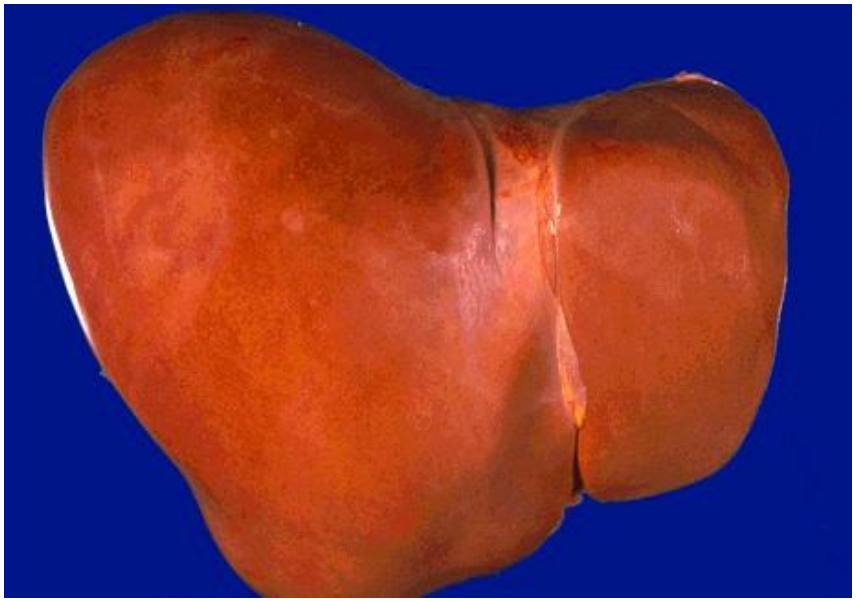
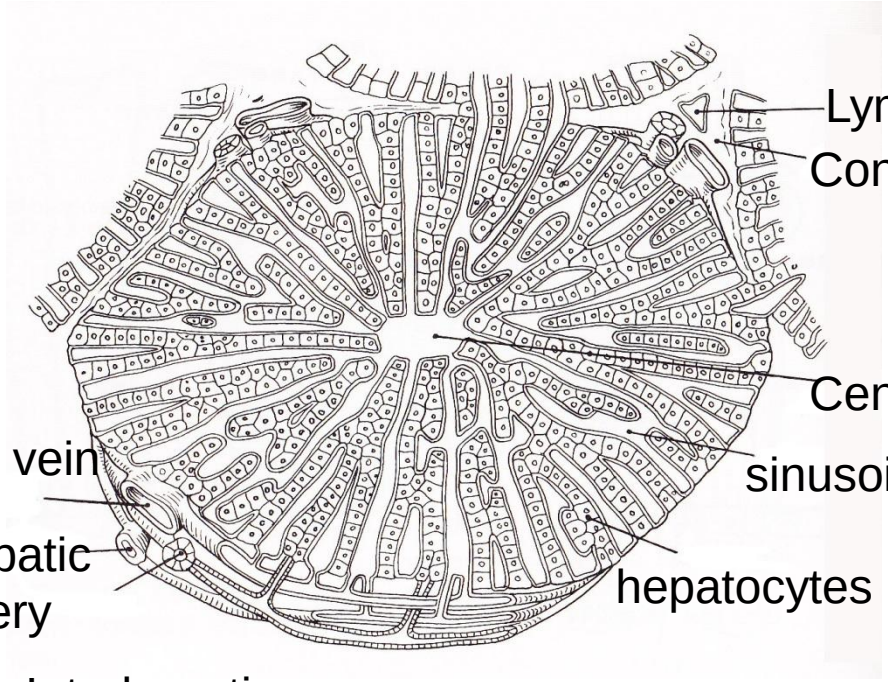
Anatomy



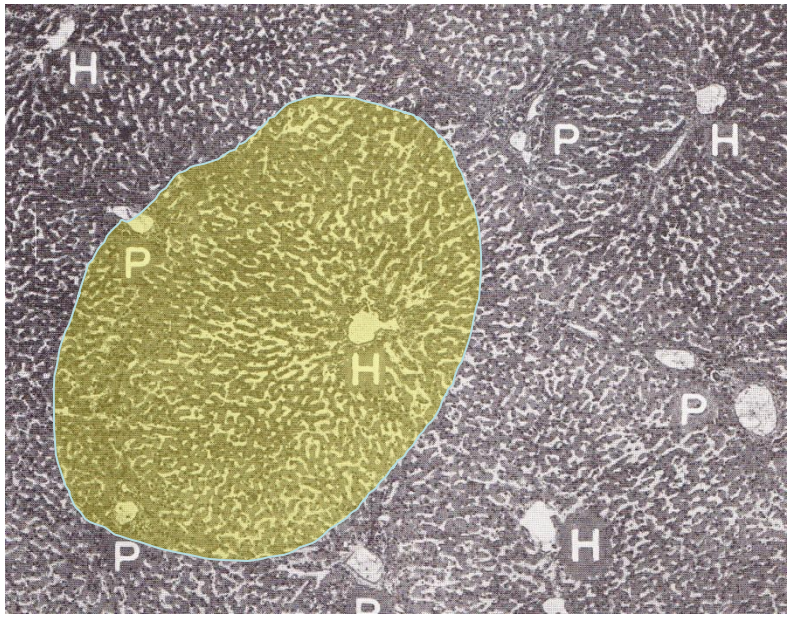
- The largest organ in the body (1200 – 1500g)
- Lies in the right upper quadrant
- Pyramid like shape
- Has double blood supply: portal vein and hepatic artery

The structure of normal human liver



Hepatic lobule

consisted of a central tributary of the hepatic vein and at the periphery a portal tract containing bile duct, portal vein radicle and hepatic artery branch.



From: Sheila Sherlock, Diseases of the Liver and Biliary System

Function of the liver

- Bile production
- Metabolism of ingested nutrient
- Elimination of waste products
- Glycogen storage
- Protein synthesis

Pan CC,et.al: IJROBP 2010

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Radiation-induced liver disease (RILD)

What can happen when the liver is irradiated?

RILD

- Classic
  - anicteric hepatomegaly and ascites, ALP↑
  - occuring between 2 W – 3 M after RT
  - retrograde congenstion followed by liver failure.
- Nonclassic
  - AST↑, ALT↑, worsening of Child-Pugh score
  - occuring between 1 W – 3 M after RT

Pan CC, et al. IJROBP 76, 2010

Partial liver irradiation & RILD

Group	N	Dose (Gy)/fr	RILD (%)	Mean normal liver dose With/without RILD	Factors associated with RILD
Michigan	203	1.5Gy bid	9.4	37Gy/ 31.3Gy	Mean liver dose
Taipei	89	1.8 - 3.0	19	23Gy/ 19Gy	HBV, LC
Shanghai	109	4 – 6	15.6	24.9Gy/ 19.9Gy	LC
Guangdong	94	4 – 8	17	N.S.	LC
Korea(Seong)	153	1.8	7	N.S.	Dose
Korea(Kim)	105	2.0	12.3	25.4Gy/ 19.1Gy	Liver volume V30*

* Total liver volume receiving 30 Gy or more above 60%

Modified from Pan CC, et al. IJROBP 76, 2010

Recommended dose-volume limits

by Pan CC

For 5% or less risk of RILD

- Partial liver RT with standard fractionation
  - Mean normal liver dose (liver – GTV)
    - < 28Gy in 2-Gy fr. for primary liver cancer
    - < 32 Gy in 2-Gy fr. for liver metastasis
- SBRT with 3 -6 fractions
  - Mean normal liver dose (liver – GTV)
    - < 13Gy / 3fr. for primary liver cancer
    - < 18Gy/ 6fr. for liver metastasis
    - < 6Gy (w. 4-6Gy/fr.) for Child-P B, HCC
    - >= 700ml of normal liver receives =< 15Gy/3-5fr.
    - etc.

Pan CC, et al. IJROBP 76, 2010

- How about particle therapy?

Dose-volume histogram analysis of proton beam therapy for unresectable hapatocellular carcinoma

Kawashima M., et al. IJROBP 79, 2011

- Single nodular or single CTV encompassing multiple lesions
- ICG R15: < 20/ 20-50/ > 50 = 20/ 32/ 8
- Tumor size: median 45mm (20 – 90)
- PBT: 76CGE/20fr., 65CGE/26fr., 60CGE/ 10fr.
- Proton-induced hepatic insufficiency (PHI)
  - hepatic insufficiency presented with anicteric ascites and/or asterixis within 6 M. after completion of PRT in the absence of disease progression

Dose-volume histogram analysis of proton beam therapy for unresectable hapatocellular carcinoma

Kawashima M., et al. IJROBP 79, 2011

- ICG R 15 < 20%
  - No PHI
- ICG R 15 20 – 50%
  - should minimize the irradiated volume
  - V30 < 25% in the noncancerous portion of the liver
- ICG R 15 > 50%
  - Indication of PBT is limited

Evaluation of liver function after proton beam therapy for hepatocellular carcinoma.

Mizumoto M. et al, IJROBP 2012

- 259 patients, 2001 -2007
- CTV encompassing all active lesions
- Child A/ B/ C = 198/ 58/ 3
- Tumor size : median 34 mm (6 – 130)
- PBT: 77GyE/ 35fr., 72.6Gy/ 22fr., 66GyE/ 10fr.
- Adverse event: increase of >=1 in Child-Pugh score

Evaluation of liver function after proton beam therapy for hepatocellular carcinoma.

Mizumoto M. et al, IJROBP 2012

- 91/ 259 : no disease progression for 12 Mo.
  - 66/ 91 : no increase of Child-Pugh score
  - 15/ 91 : 1 point increase of CP score
  - 10/ 91 : >=2 point increase of CP score
- Optimal cut-off
  - V0/ V10/ V20/ V30 = 30%/ 20%/ 26%/ 18%
  - (Kawashima's report: V30 < 25%)
- Liver function after PBT is significantly related to the percentage volume of normal liver that is not irradiated.

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Neoplasms in the liver

Classification of Liver Cancer

Liver Cancer Study Group of Japan

- Primary liver cancer
  - Hepatocellular Carcinoma (HCC)
  - Intrahepatic Cholangiocarcinoma (CCC)
  - Combined HCC & CCC
  - Cystadenocarcinoma
  - Hepatoblastoma
- Metastatic Liver cancer
  - Colon, Rectum, Breast etc.

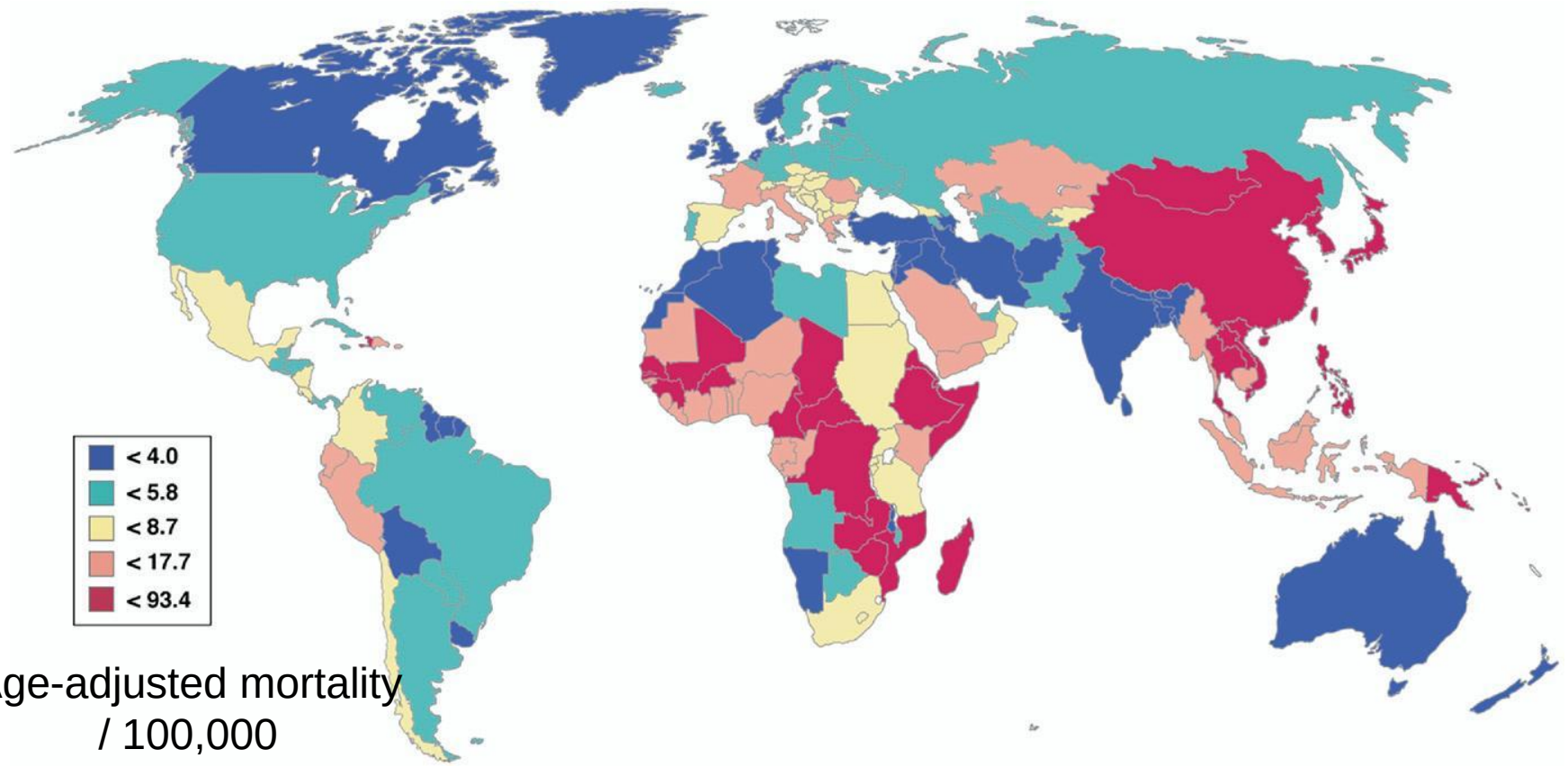
- Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality.
- Hepatocellular carcinoma (HCC) accounts for between 85% and 90% of primary liver cancers.

Today's talk will be focused on HCC

Epidemiology of HCC

- Variations among geographic regions, racial and ethnic groups
- Men : Women = 2 : 1 – 4 : 1
- Environmental potentially preventable risk factors

Regional variations in the mortality rates of HCC



El-Serag HB, Gastroenterology 2007

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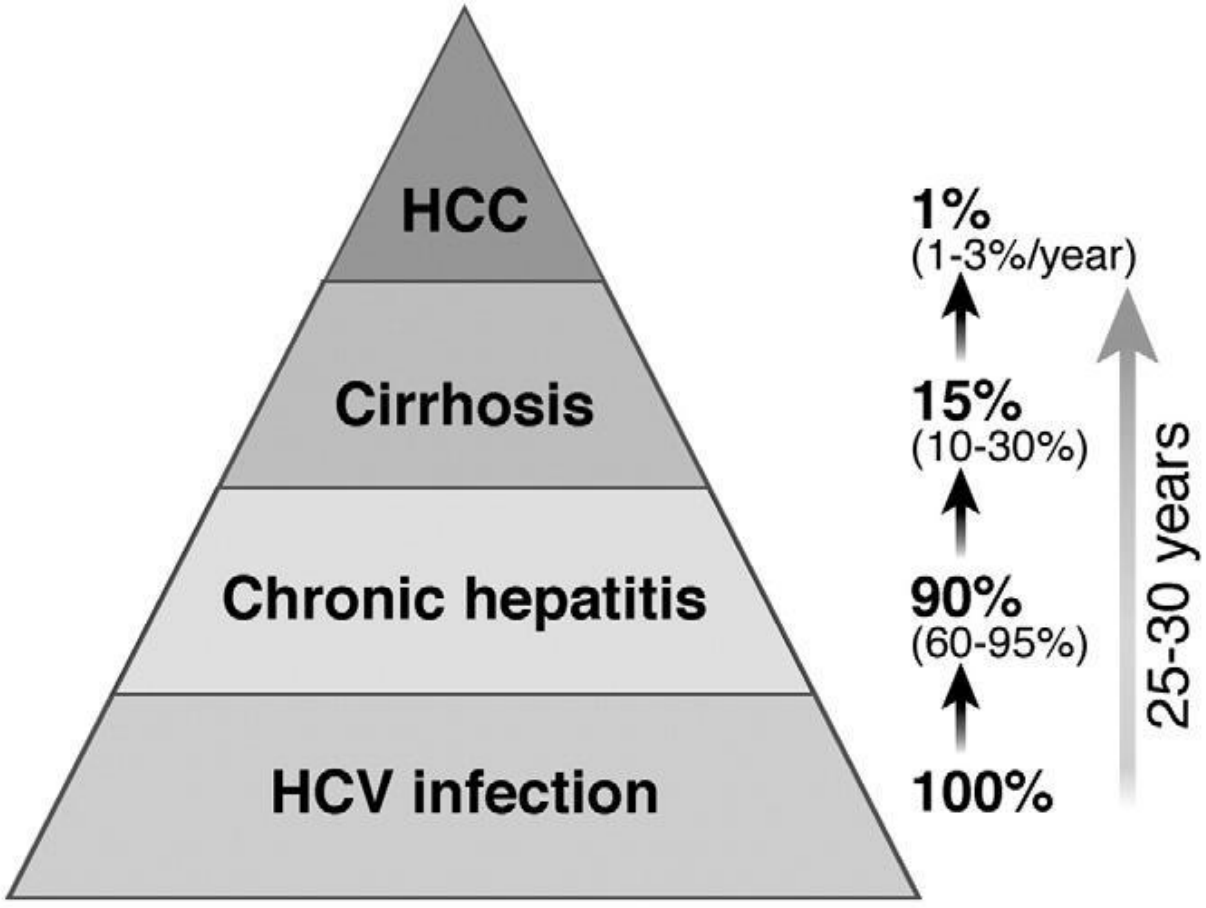
Risk factors of HCC

- Hepatitis virus infection HBV, HCV
- Alcohol
- Toxic exposure
  - Afratoxin, Vinyl chloride
- Nonalcoholic fatty liver disease (NASH)
- Obesity
- Diabetes Mellitus

Proportion of patients with HCC related to HCV viral hepatitis



Hassan MM, J Clin Gastroenterol 2002

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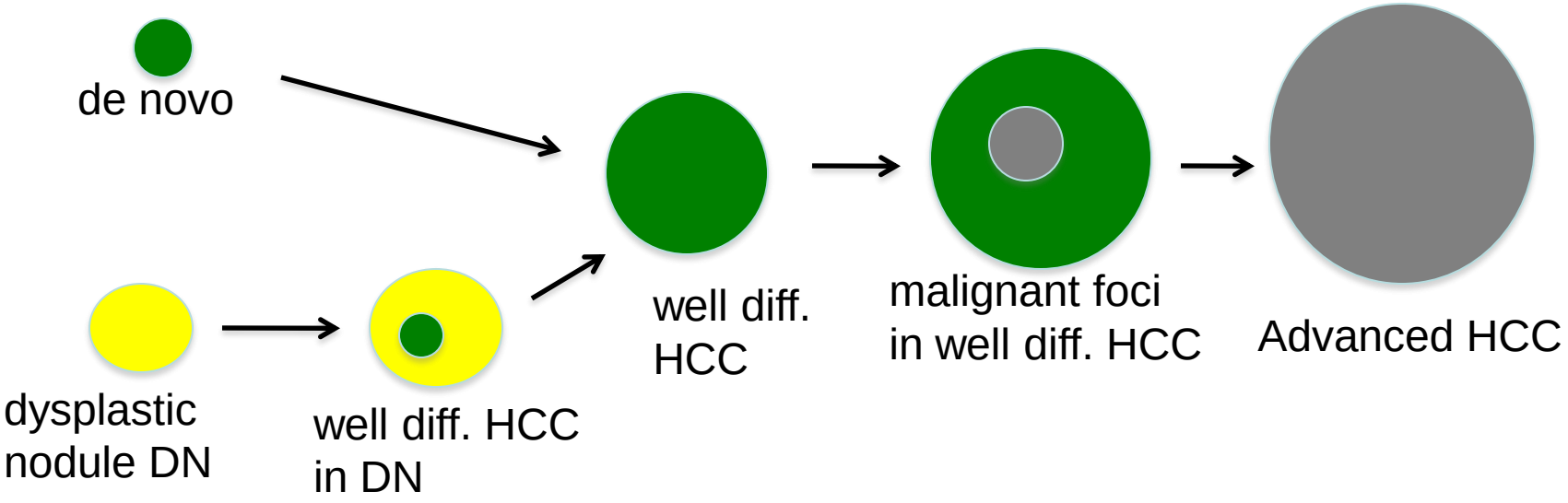
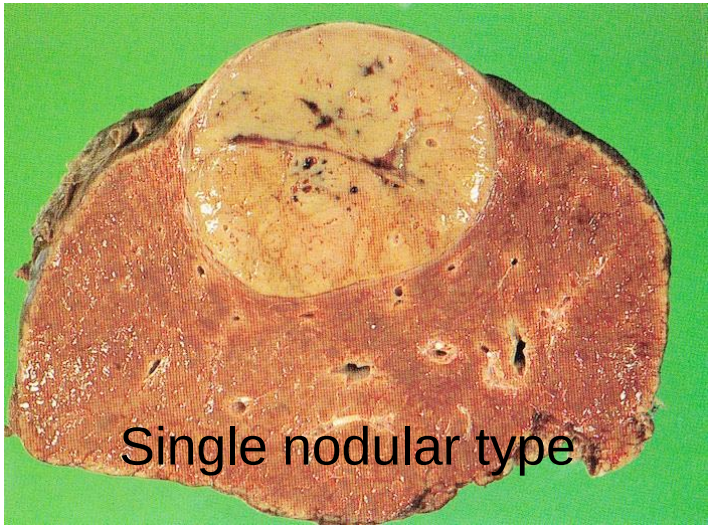
Two types of human hepatocarcinogenesis

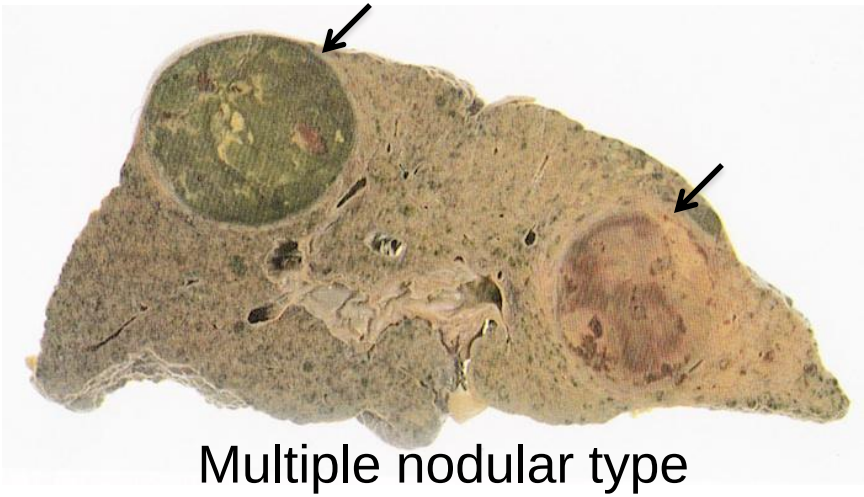


- Upper: de novo hepatocarcinogenesis
- Lower: stepwise development from high-grade DN, high-grade DN with well-differentiated HCC foci, and overt HCC

Modified from Matsui O, Radiology 1991

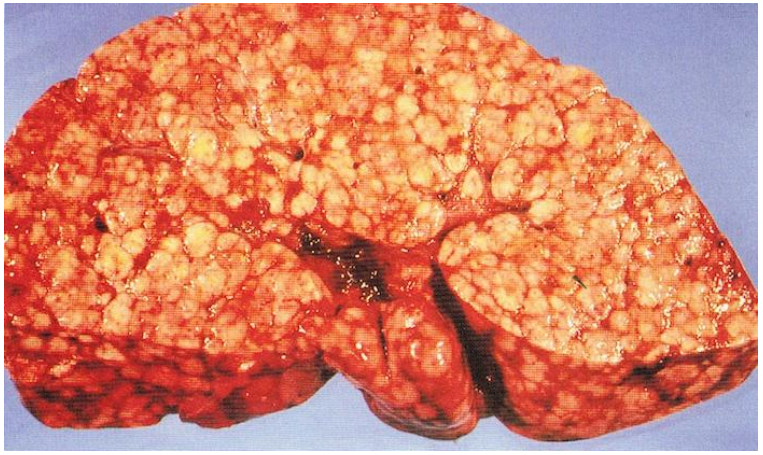
Macroscopic types of HCC





Multiple nodular type

Massive type



Diffuse type

Classification of Primary Liver Cancer: Liver Cancer Study Group of Janan

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Treatment options for HCC

- Surgical resection
  - The mainstay Tx but majority are not eligible
- Liver transplantation
  - Solitary, < 5cm or < 3 nodules, < 3cm
- Percutaneous ablation: RFA, PEI
  - < 3 nodules, < 3 cm
- Transcatheter Arterial Chemoembolization
  - Suitable for multiple, unresectable HCC
- Radiotherapy: particles, SBRT, Y90-IRT

Cohort study conducted by Liver Cancer Study Group Japan

OS by various standard treatment for HCC

		n	1 year	3 year	5 year
surgery	radical	19845 (25066)	91.9	74.6	58.9
RFA	Solitary tumor	6474 (9643)	95.7	80.0	61.7
TACE	Solitary tumor	7942 (31600)	83.6	54.6	32.4

Data are from most favorable group of patients

(2009)

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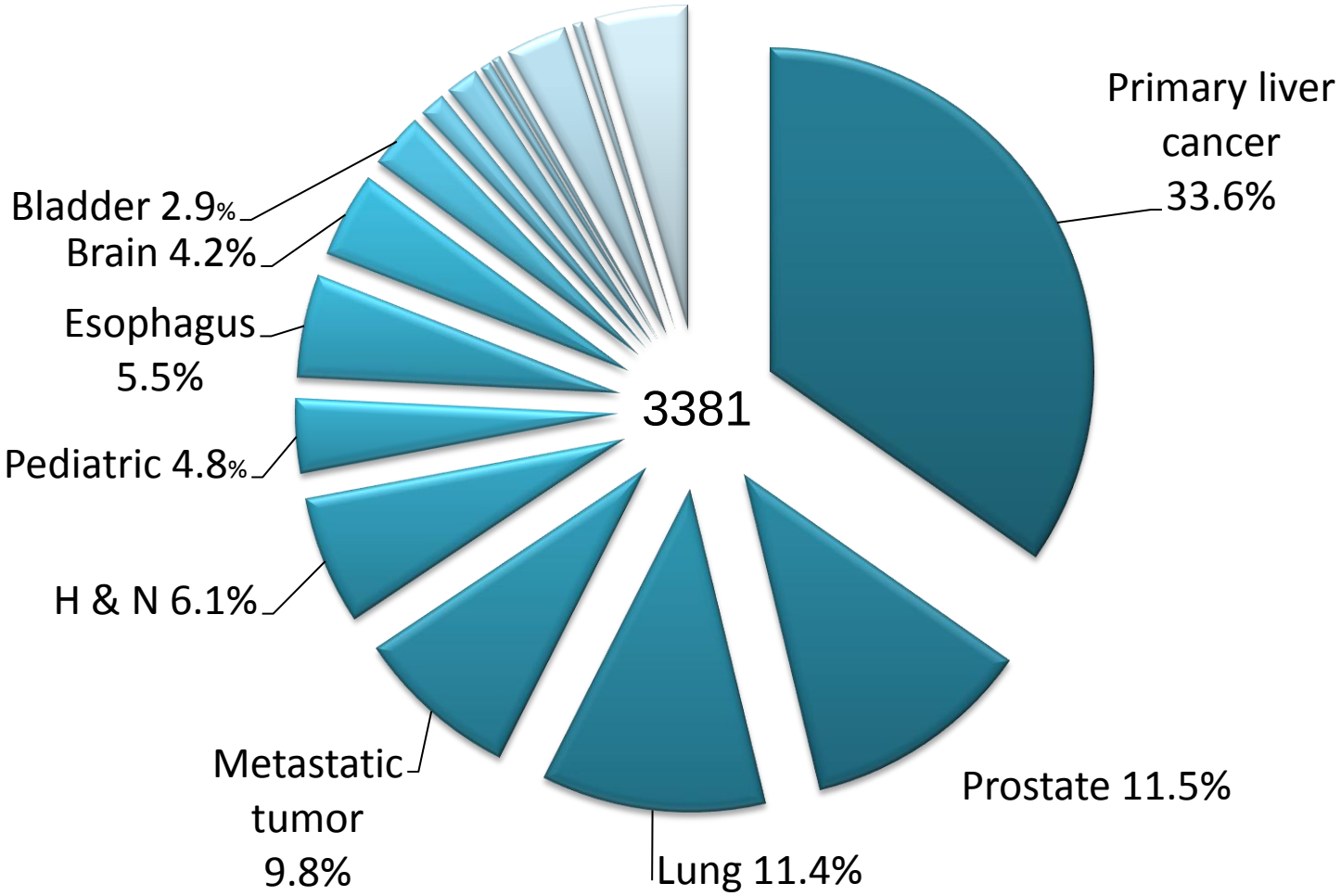
PBT for Hepatocellular Carcinoma

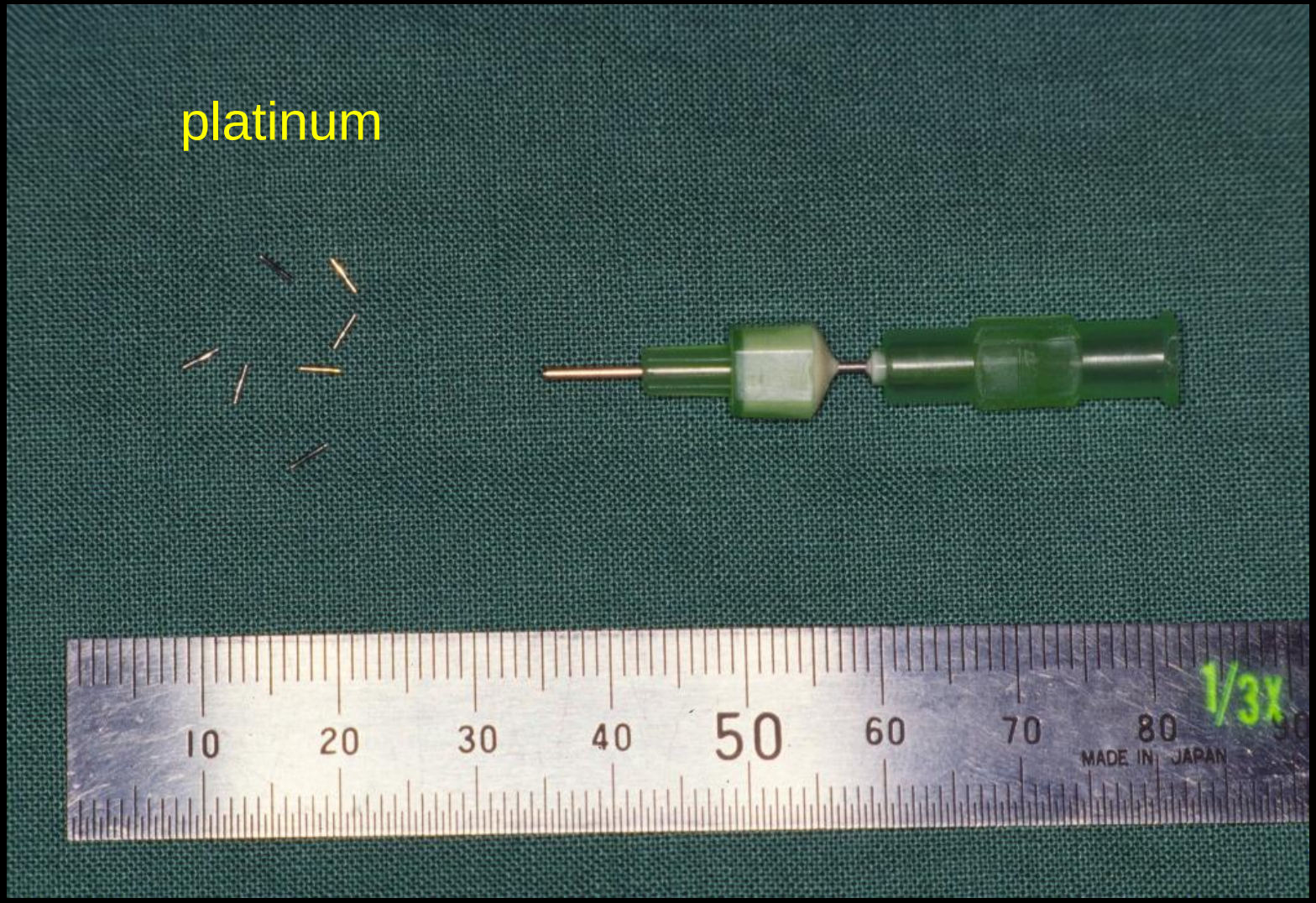
Cases at PMRC, Tsukuba (1983 – 2013.3)



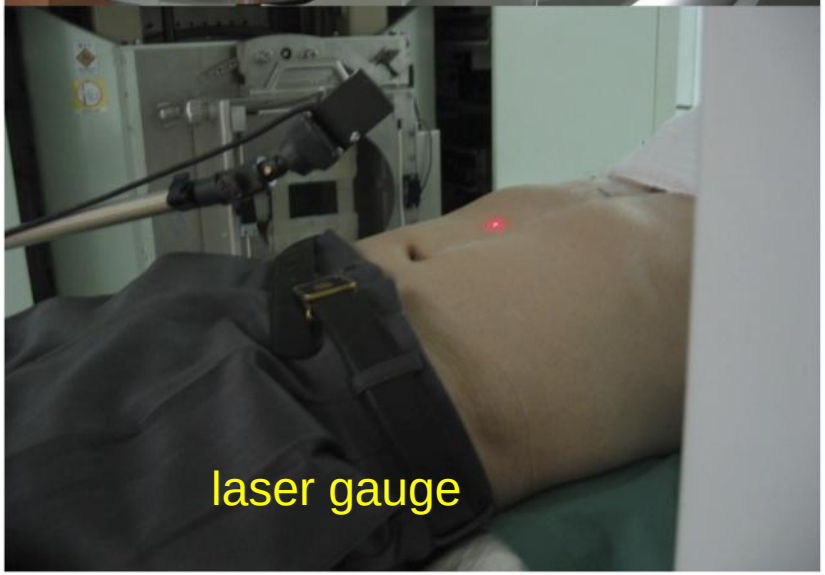
Standard procedure for treating liver tumors @ PMRC

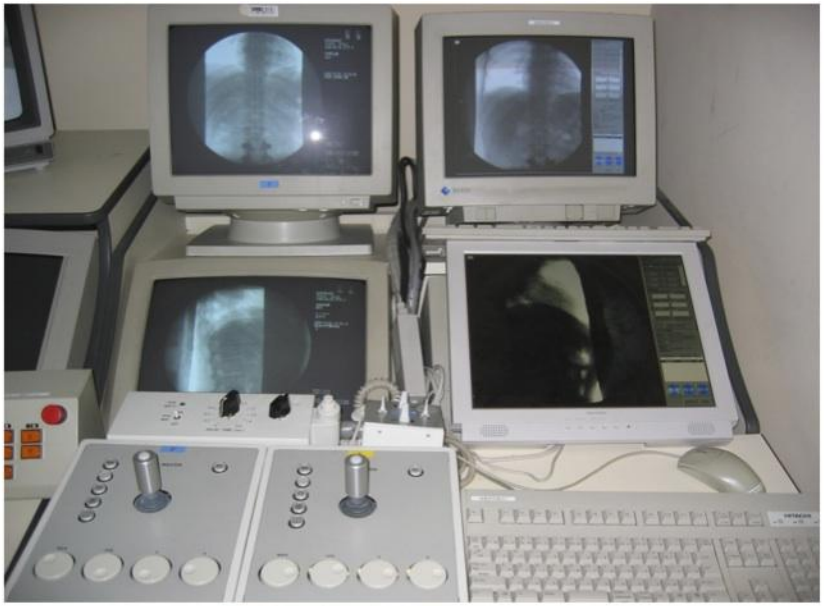
- Fiducial marker implant under ultrasonographic guidance
- Real-time tumor localization using fluoroscope
- Respiratory gated irradiation

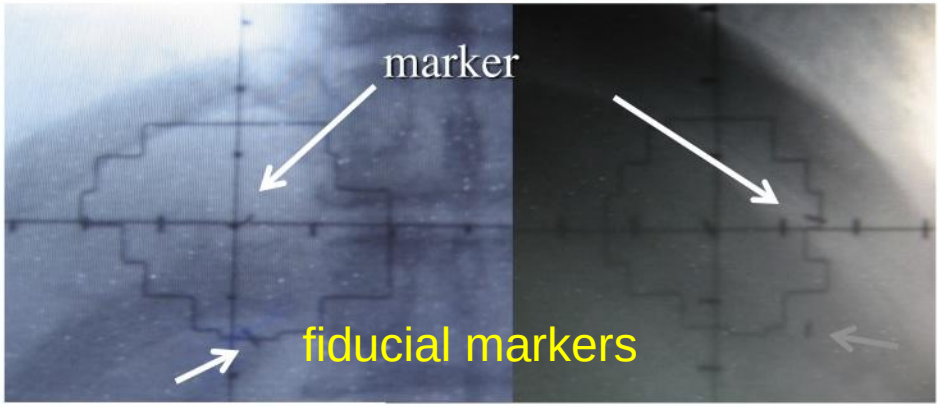
In-situ fiducial marker



A fiducial marker is used to adjust the daily positioning under the respiratory gating.



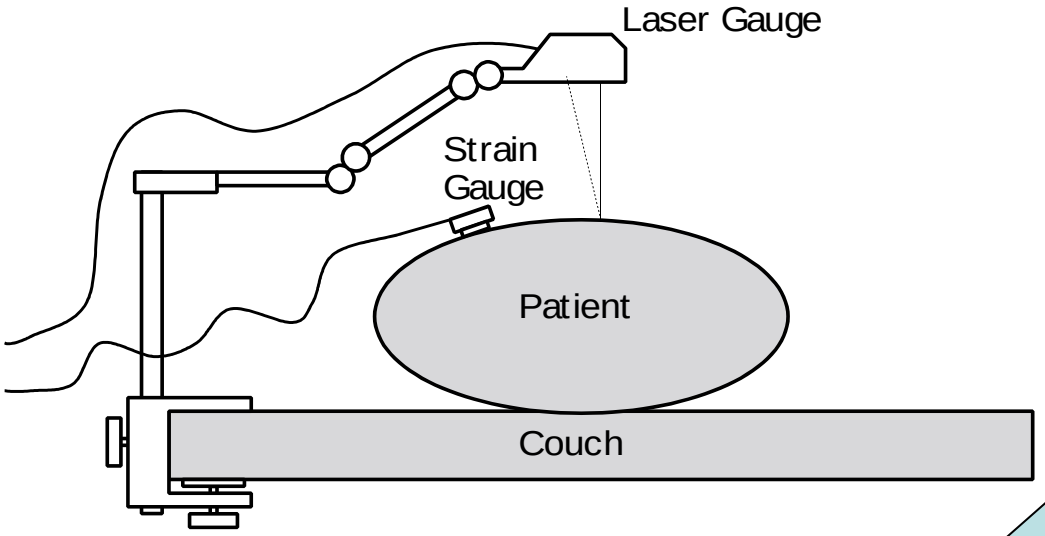


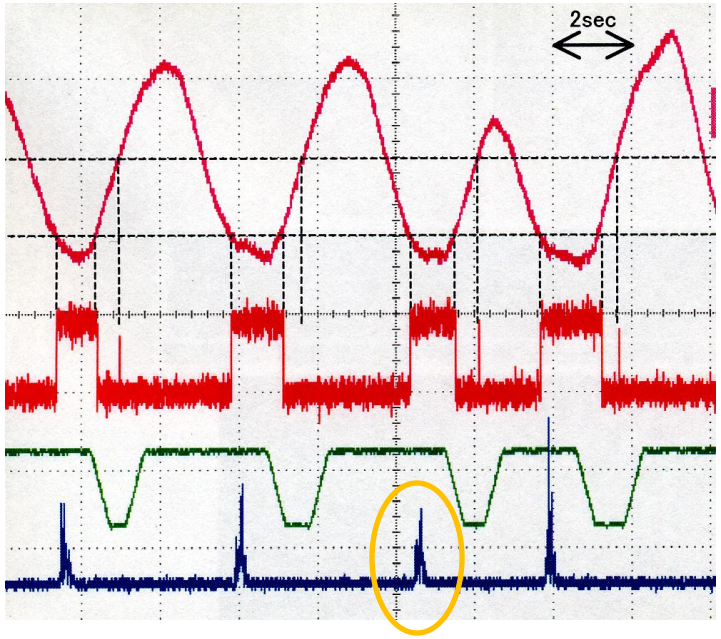


Internal Target Volume (ITV) of the liver

- >= 2 cm displacement during regular breathing (mostly C-C direction)
- Management for RT
  - Abdominal compression
  - Shallow breathing
  - Breath holding
  - Deformation modeling
  - Gated treatment
  - Real-time tumor tracking

Respiratory gated irradiation





Respiratory wave

Trigger and pre-trigger

Beam signal (Proton beams were released during the expiratory phases)

Dose, fractionation according to tumor location

	Tumor location	dose/ fraction	EQD_2 α/β: 10
Ex	Standard @ PMRC_KEK for peripheral type	79.2 GyE/ 16fr	98.7 Gy
A	Peripheral type	66 GyE/ 10fr	91.3 Gy
B	Central type	72.6 GyE/ 22fr	80.5 Gy
C	Close to GI	77 (74)GyE/ 35 (37) fr	78.3 (74)Gy

(*): since 2008

Dose, fractionation according to tumor location

	Tumor location	dose/ fraction	EQD_2 α/β: 10
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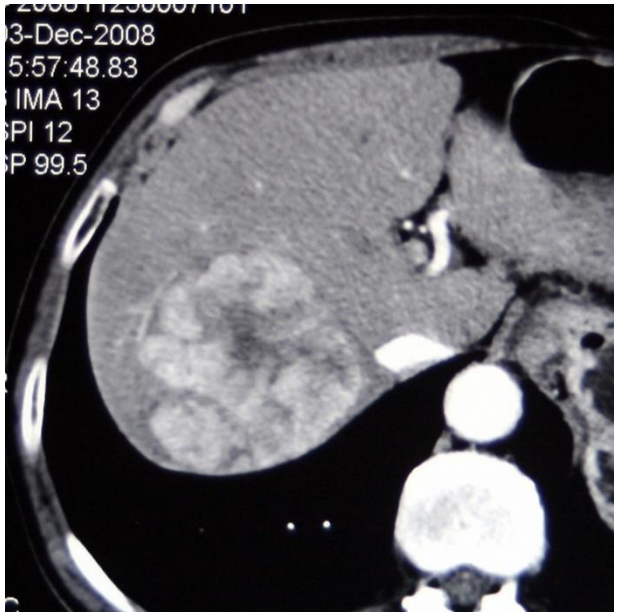
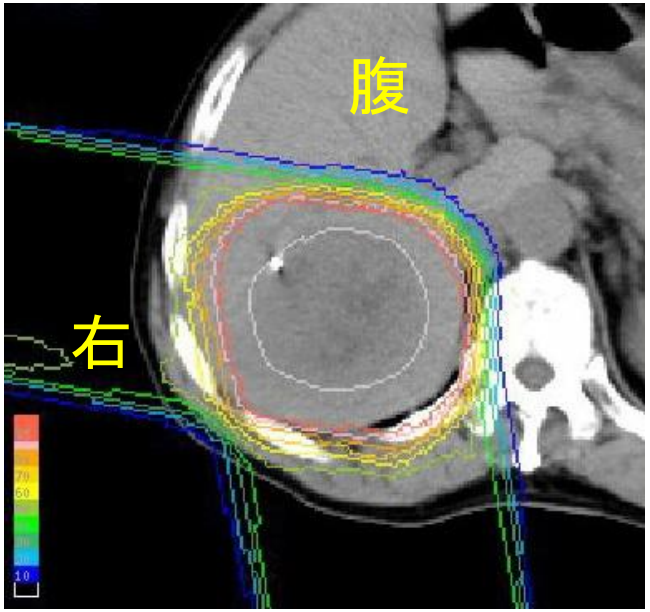
(*): since 2008

Dose distribution for a peripheral type HCC

A



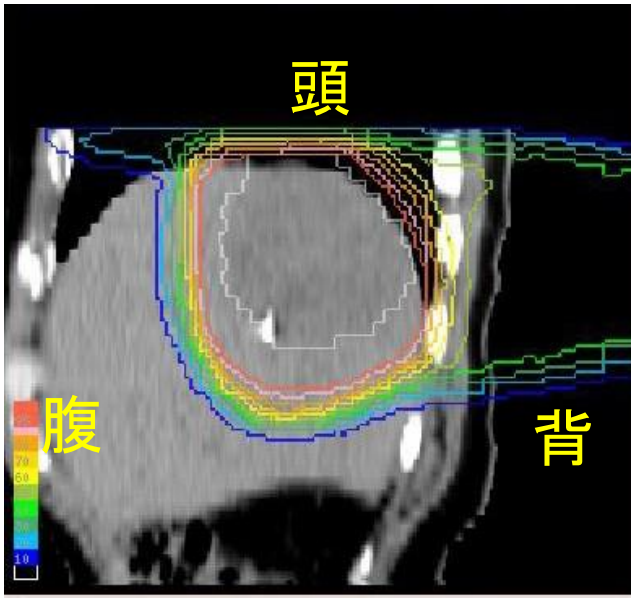
B



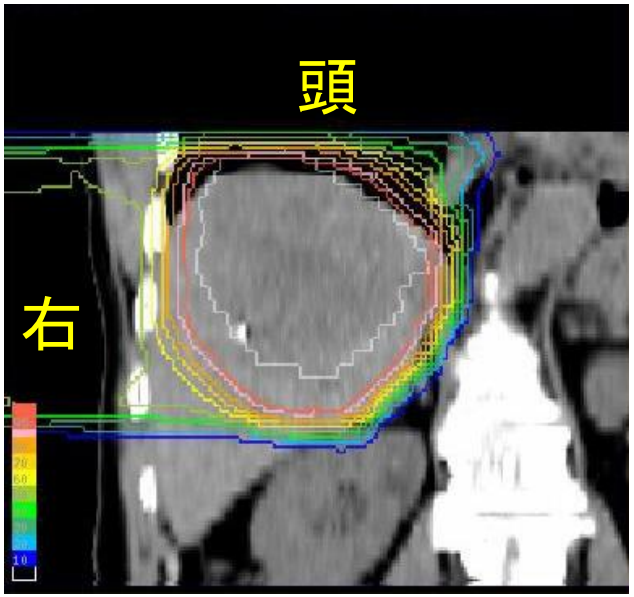
white
GTV

red
100% dos

C

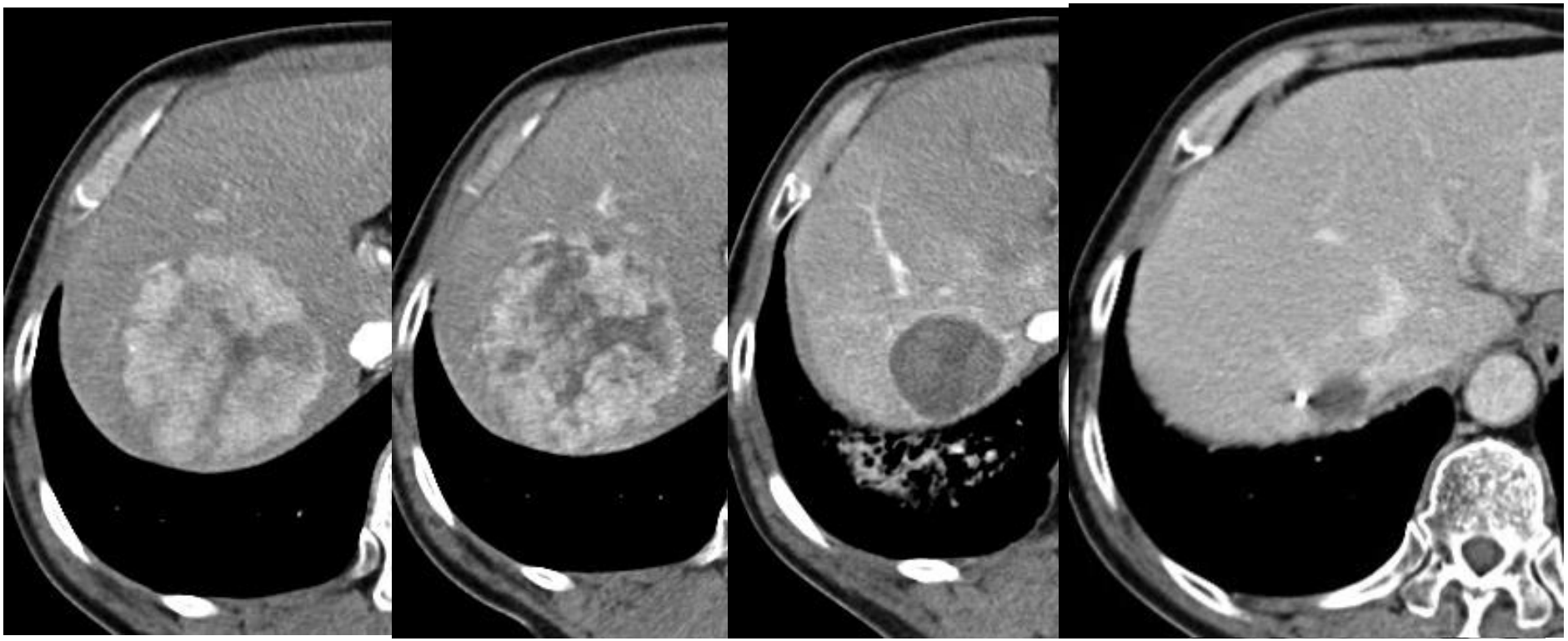


D



blue
10% dose

Hepatocellular carcinoma peripheral type： 66GyE/ 10fr./ 15D



pre PBT

2 months after PBT

4 months

46 months

Dose, fractionation according to tumor location

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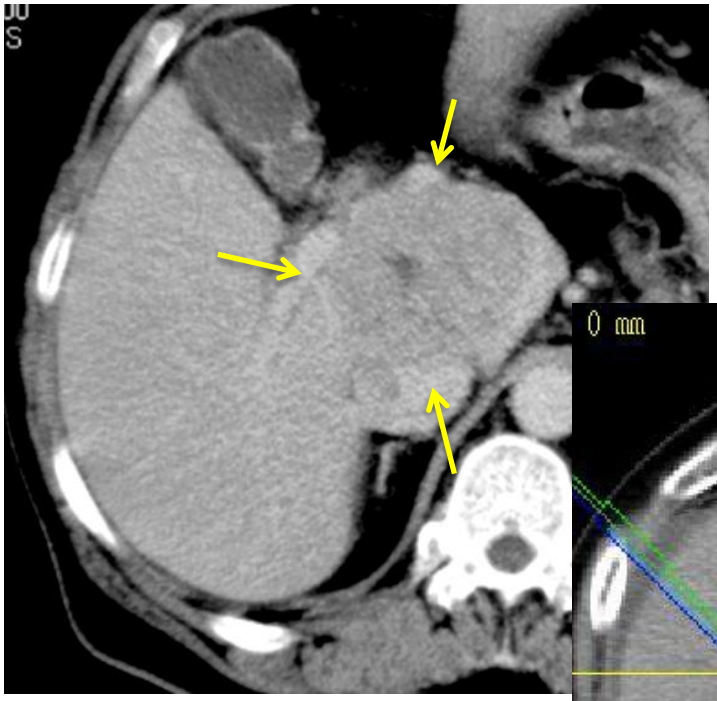
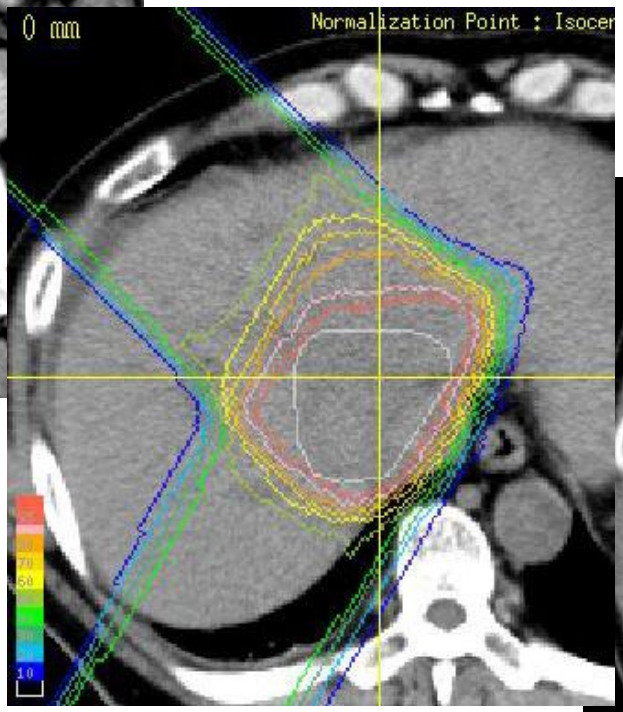
(*): since 2008

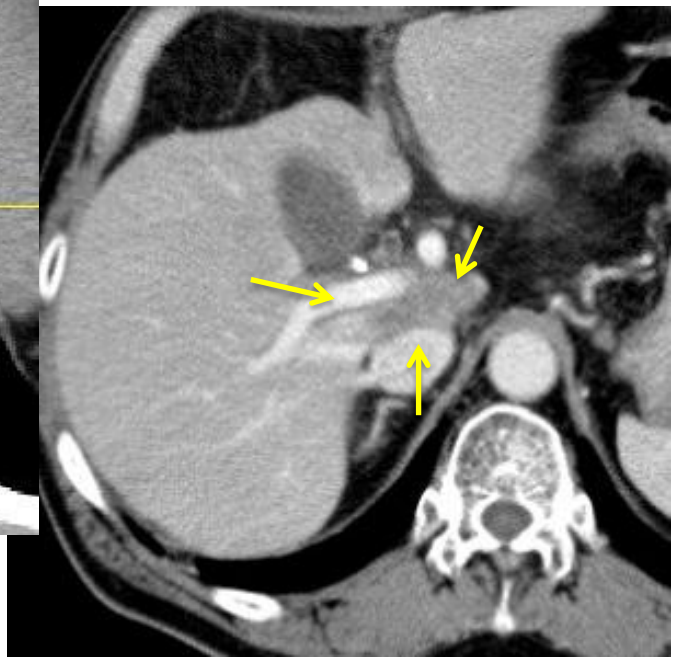
Central type HCC
72.6GyE/ 22fr.





Pre PBT

post PBT 8 Mo.



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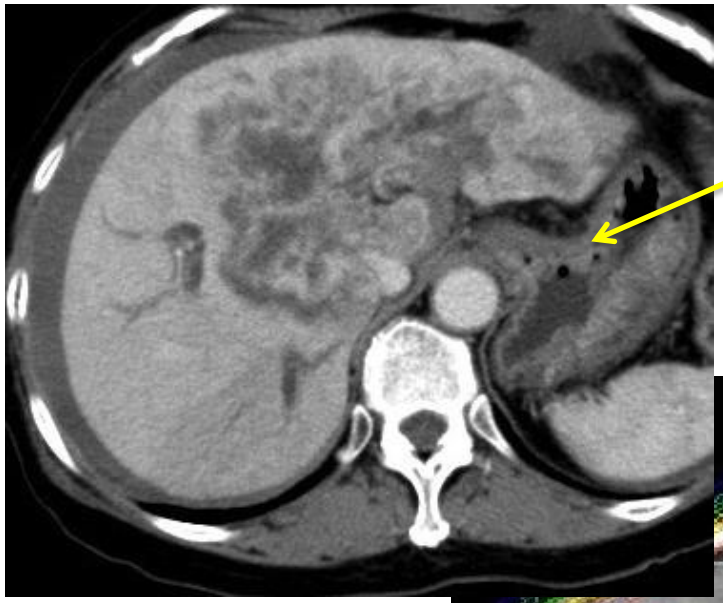
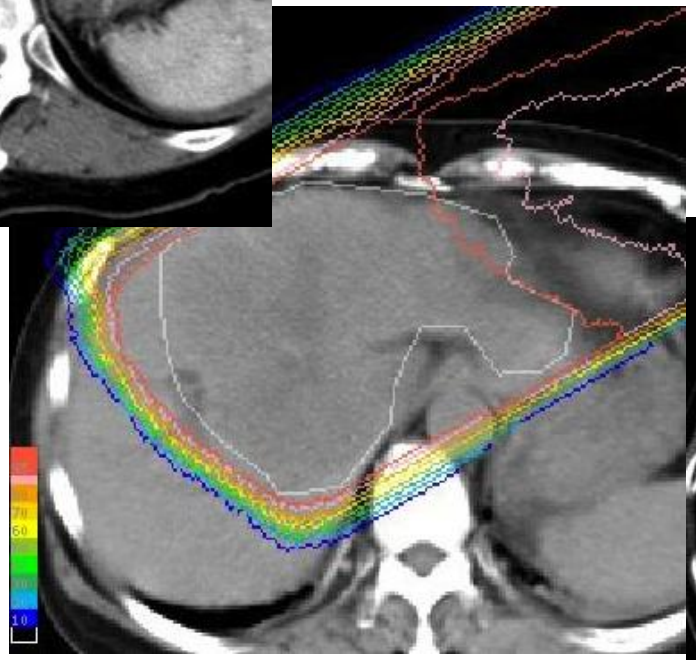
(*): since 2008

Tumor close to the GI tract



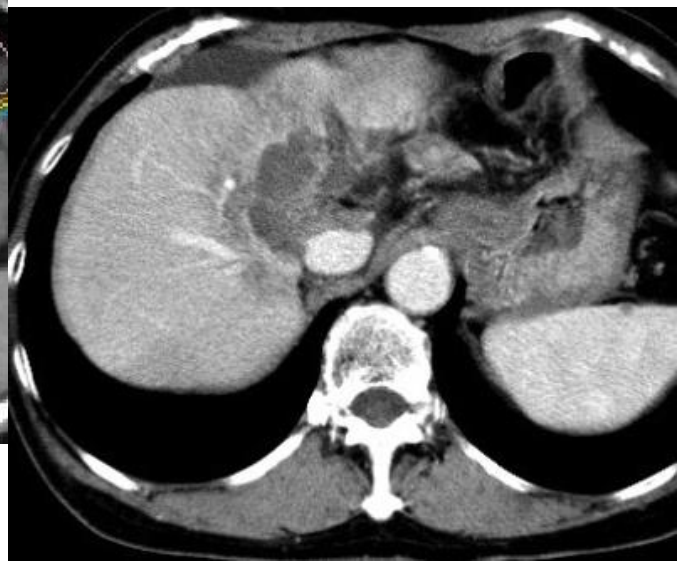
Gastroesophageal junction

pre PBT



74GyE/ 37fr.

1 Y after PBT



Clinical results

Proton Beam Therapy for Hepatocellular Carcinoma: A Comparison of Three Treatment Protocols

Mizumoto M, et al: IJROBP 2011; 81: 1039-1045

- Period: 2001 Jan. – 2007 Dec.
- Eligibility criteria
  - No active tumor outside the target volume
  - PS <=2
  - Child-Pugh score <=10
  - No extrahepatic metastasis
  - WBC => 1000/mm^3, Hgb => 6.5 g/dl, Plt => 25000/mm^3

Proton Beam Therapy for Hepatocellular Carcinoma: A Comparison of Three Treatment Protocols

Mizumoto M, et al: IJROBP 2011; 81: 1039-1045

- N= 266 (66GyE: 104, 72.6GyE: 95, 77GyE: 60)
- OS @ 1/ 3/ 5 yr. : 87%/ 61%/ 48%
- Local control @ 1/ 3/ 5 yr. : 98%/ 87%/ 81%
- No significant difference between the protocols
- Predictive factors for OS: liver function, small CTV, no prior treatment

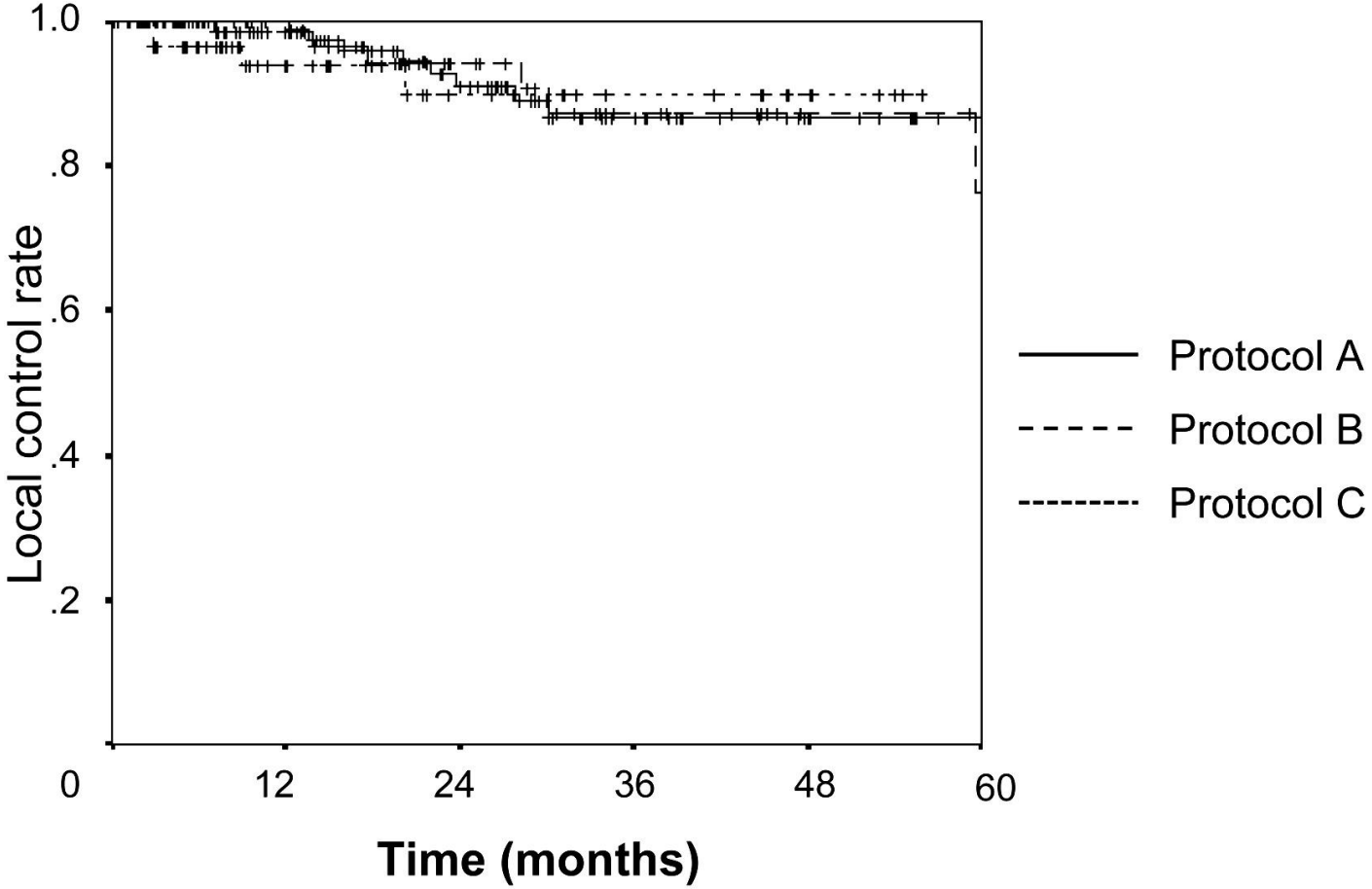
toxicity

Acute	**dermatitis**	**Grade 1**	**127**
		Grade 2	**12**
		Grade 3	**2**
Late	**Rib fracture**		**3**
	dermatitis	**Grade 1**	**2**
		Grade 3	**1**
	Gastro intestinal*	**Grade 2**	**3**
		Grade 3	**3**

*: all were “ close to GI “ type

Mizumoto IJROBP 81, 2011

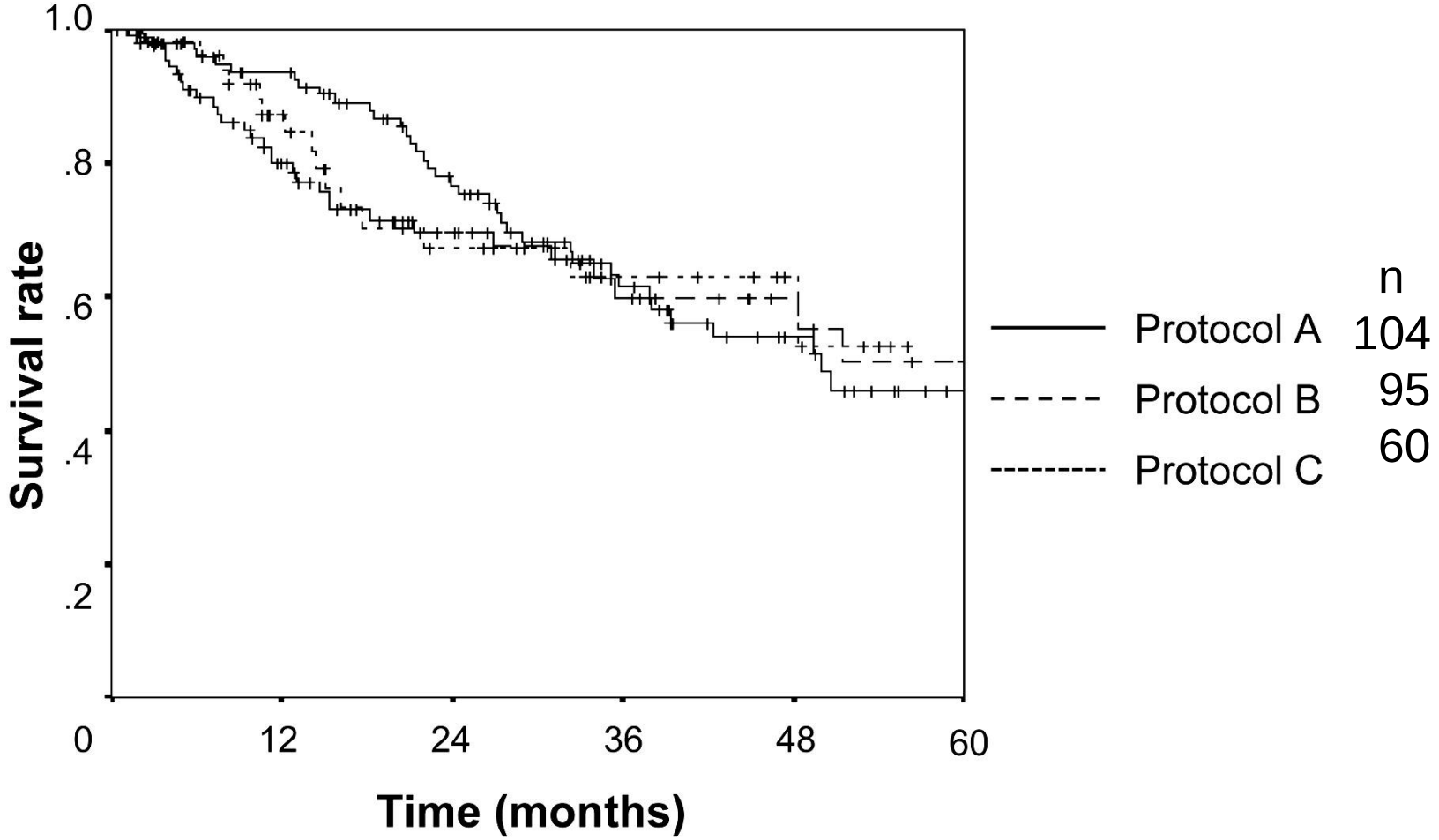
Local control rates for 273 tumors



Local control @ 1/ 3/ 5 yr. : 98%/ 87%/ 81%

Mizumoto IJROBP 81, 2011

Overall survival rates for 259 patients



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Mizumoto IJROBP 81, 2011

Cohort study conducted by Liver Cancer Study Group Japan (2009)

		n	1 year	3 year	5 year
surgery	radical	19845 (25066)	91.9	74.6	58.9
RFA	Solitary tumor	6474 (9643)	95.7	80.0	61.7
TACE	Solitary tumor	7942 (31600)	83.6	54.6	32.4
proton		259	87	61	48

Clinical results of particle therapy for HCC

Series	particle	n	dose (GyE)/Fx	ED in 2Gy/Fx	Preceding Tx	Local control	OS
Kawashima 2005	P	30	76/ 20	87.4	none	96% @2yr	66% @2yr
Bush 2004	P	34	63/ 15	74.6	none	75% @2yr	55% @2yr
Fukumitsu 2009	P	51	66/ 10	91.3	65%	94.5% @3yr	49.2% @3yr
Mizumoto 2008	P	53	72.6/ 22	80.5	72%	86% @3yr	45.1% @3yr
Kim PTCOG 2012	P	12	72 / 24	78	none	82.5% @ 3yr	70.7% @ 3yr
Kato 2004	C	24	49.5-79.5/ 15		none	81% @3yr	50% @3yr

from our experience

- The choice of fractionation schedule based on the proximity of the dose limiting structures is useful.
- Careful treatment planning should be made for the tumor close to GI tract to avoid late morbidity.

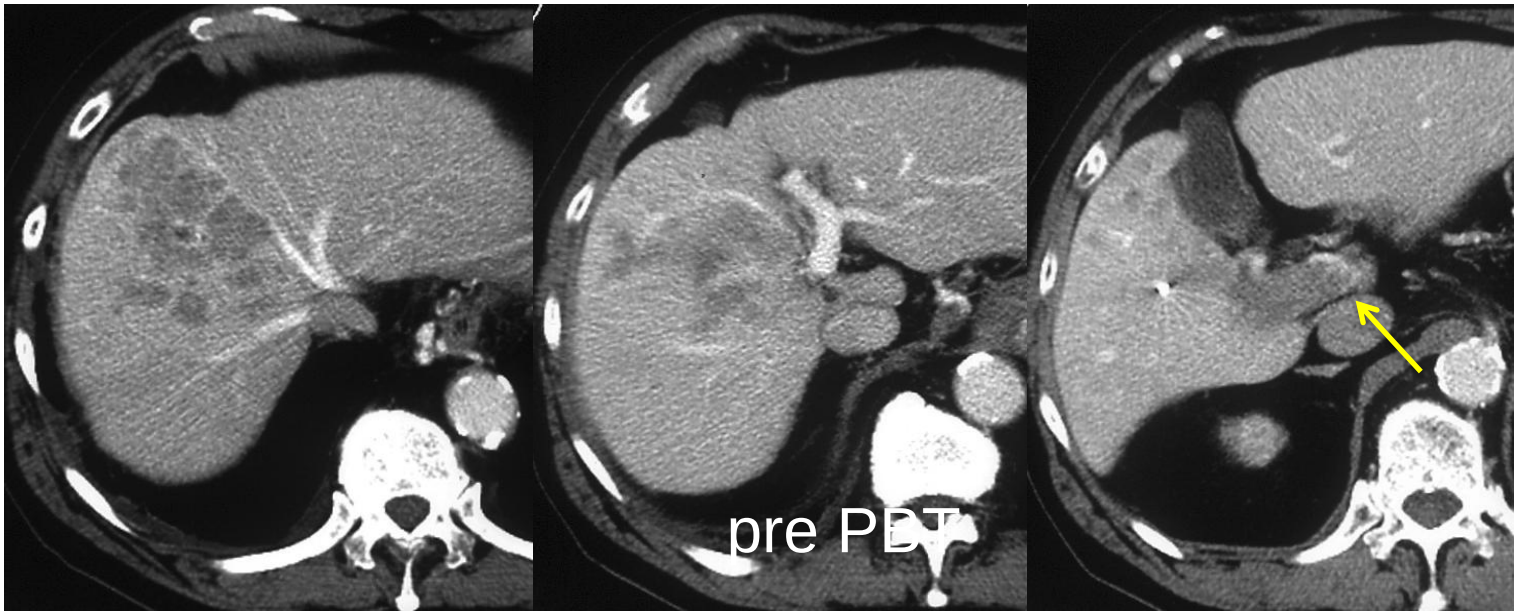
Mizumoto IJROBP 81, 2011

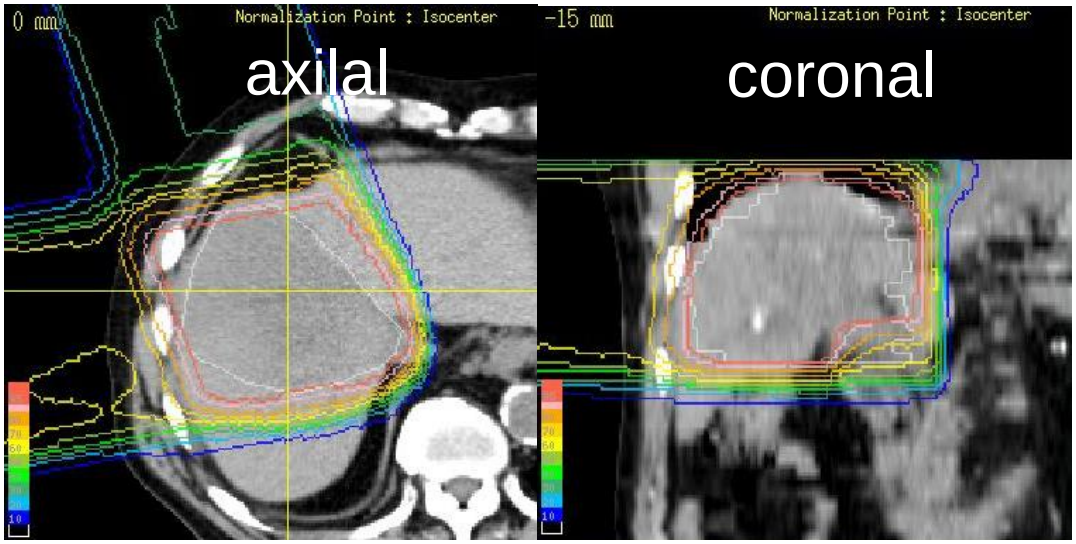
Proton-Beam Therapy for Hepatocellular Carcinoma associated with Portal Vein Tumor Thrombosis

S Sugahara, H Nakayama, K Fukuda, M Mizumoto, M Tokita, M Abei, J Shoda, Y Matsuzaki, E Thono, K Tsuboi, K Tokuuye

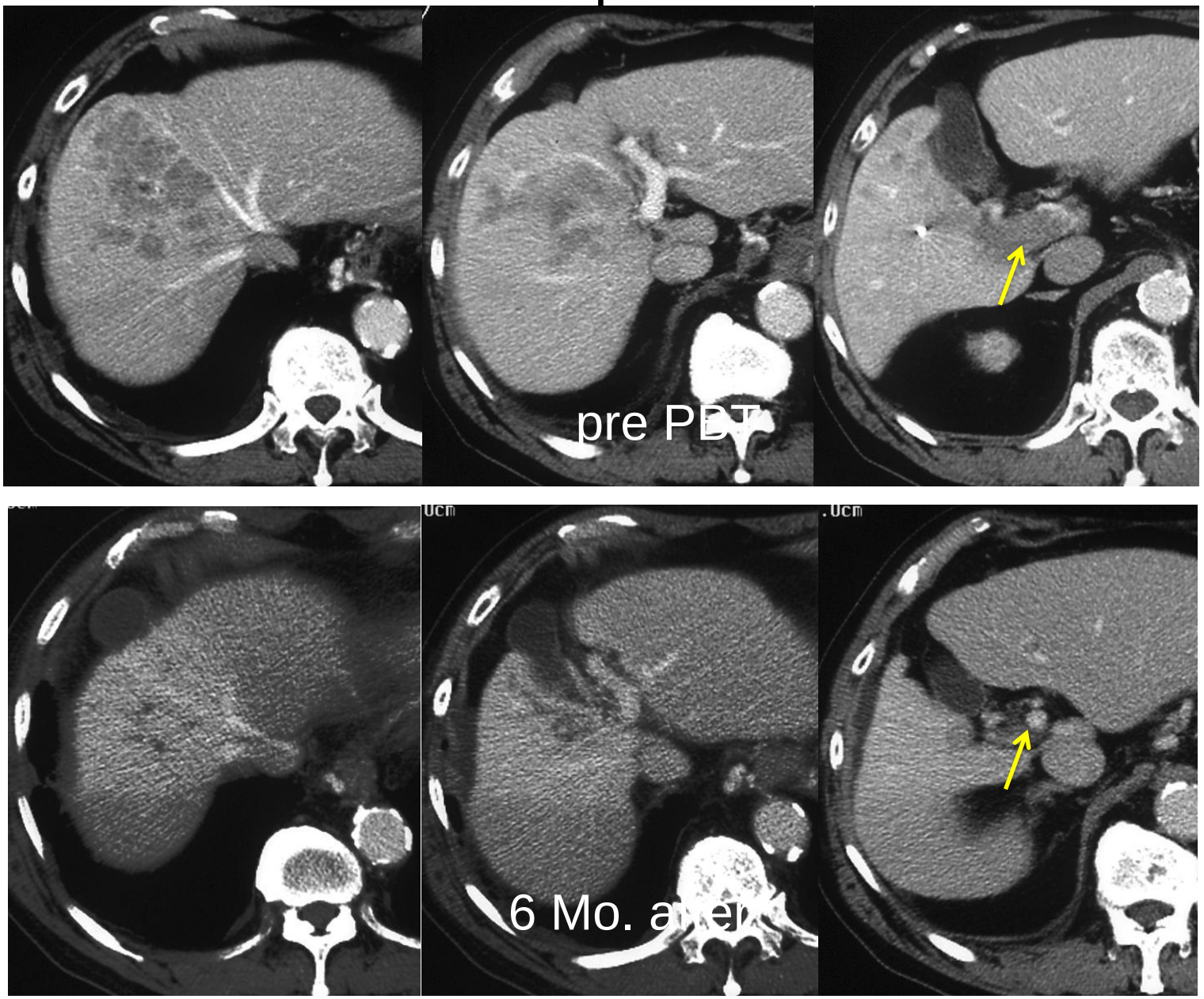
Strahlenther Onkol 2009

Central type HCC 81 yr., LC (C), Pugh score: 6, Vp4





Central type HCC 81 yr., LC (C), Pugh score: 6, Vp4



Radiation (X ray) Therapy for PVTT

Author	No.Case	PVTT	treatment method	RR*	MST(Mo.)	
Tazawa J	24	Vp3,4	TACE+RT50Gy	50	CR,PR;9.7 NC,PD;3.8	2001
Yamada K	8	Vp3	TACE+RT60Gy+TACE	38	5.7(+2)	2001
Ishikura S	20	Vp3	TACE+RT	50	5.3	2002
Nakagawa K	52	Vp2,3,4	3DCRT57Gy (39-60)	50	(25.3%;2YSR)	2005
Kim DY	59	Vp3,4	3DCRT30-54Gy	45.8	CR,PR;10.7 NC,PD;5.3	2005
Lin CS	43	Vp3,4	RT45Gy/15fr:22	75	6.0	2006
			3DCRT45Gy/25fr:21	83	6.7	

*RR: response rate

Patients and Method

- Period: February 1991 – September 2005
- Tumor thrombus in the main trunk and/or major branches of the portal vein
- No extrahepatic metastases
- Not diffusely infiltrating tumor
- Child – Pugh score: A or B
- PS: 0-1

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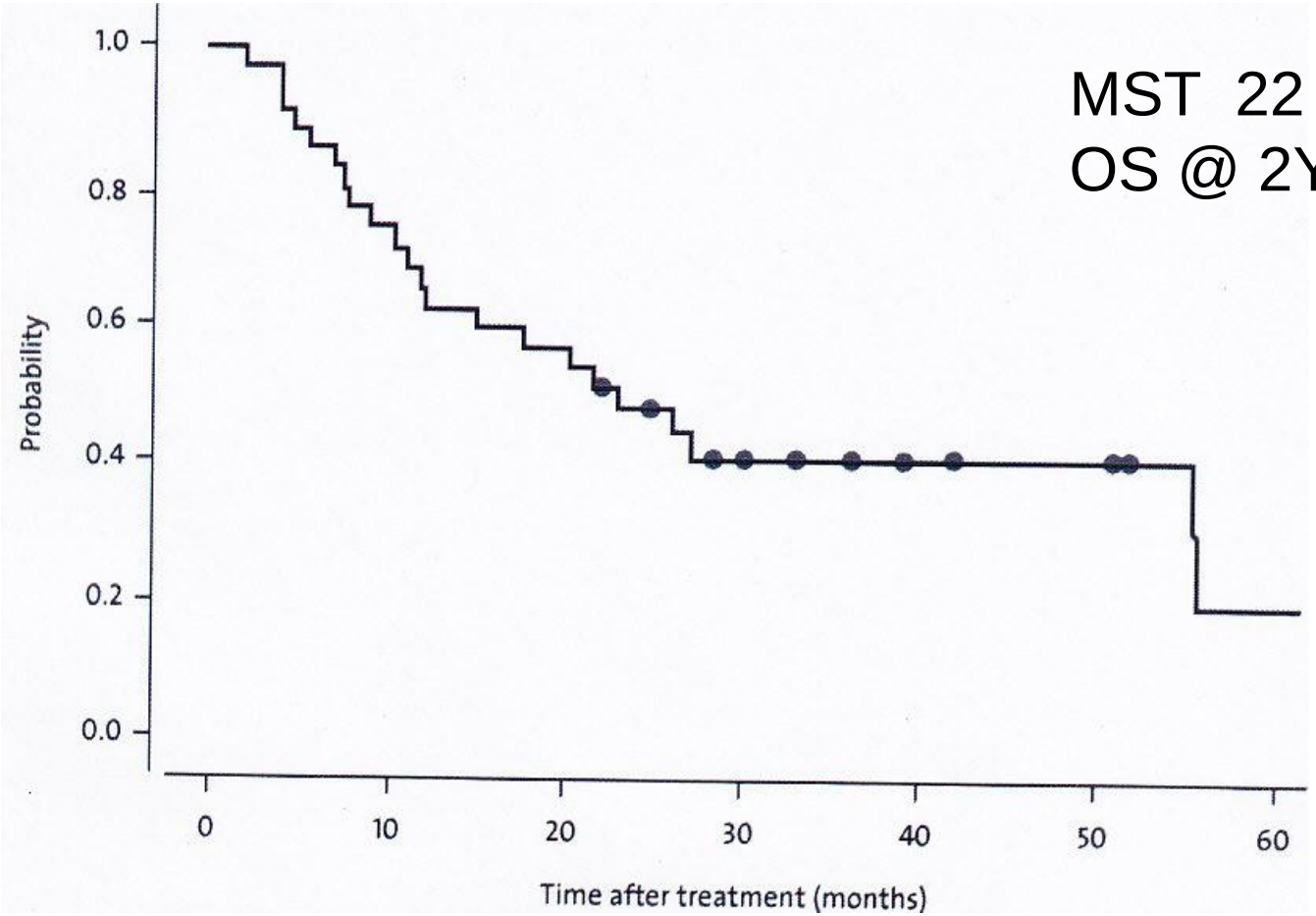
Overall survival for all 35 cases



MST 22 months
OS @ 2Y: 48%

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Results

Alive :15	Progression-free	5
	Relapse	
	New lesions outside of the PTV	9
	Marginal recurrence	1
Dead : 20	Cancer Death (HCC	15
	Liver failure	2
	Rupture of esophageal varices	1
	Accidental death	1
	Dead from esophageal cancer	1

Median survival: 22 months (2-88 months)

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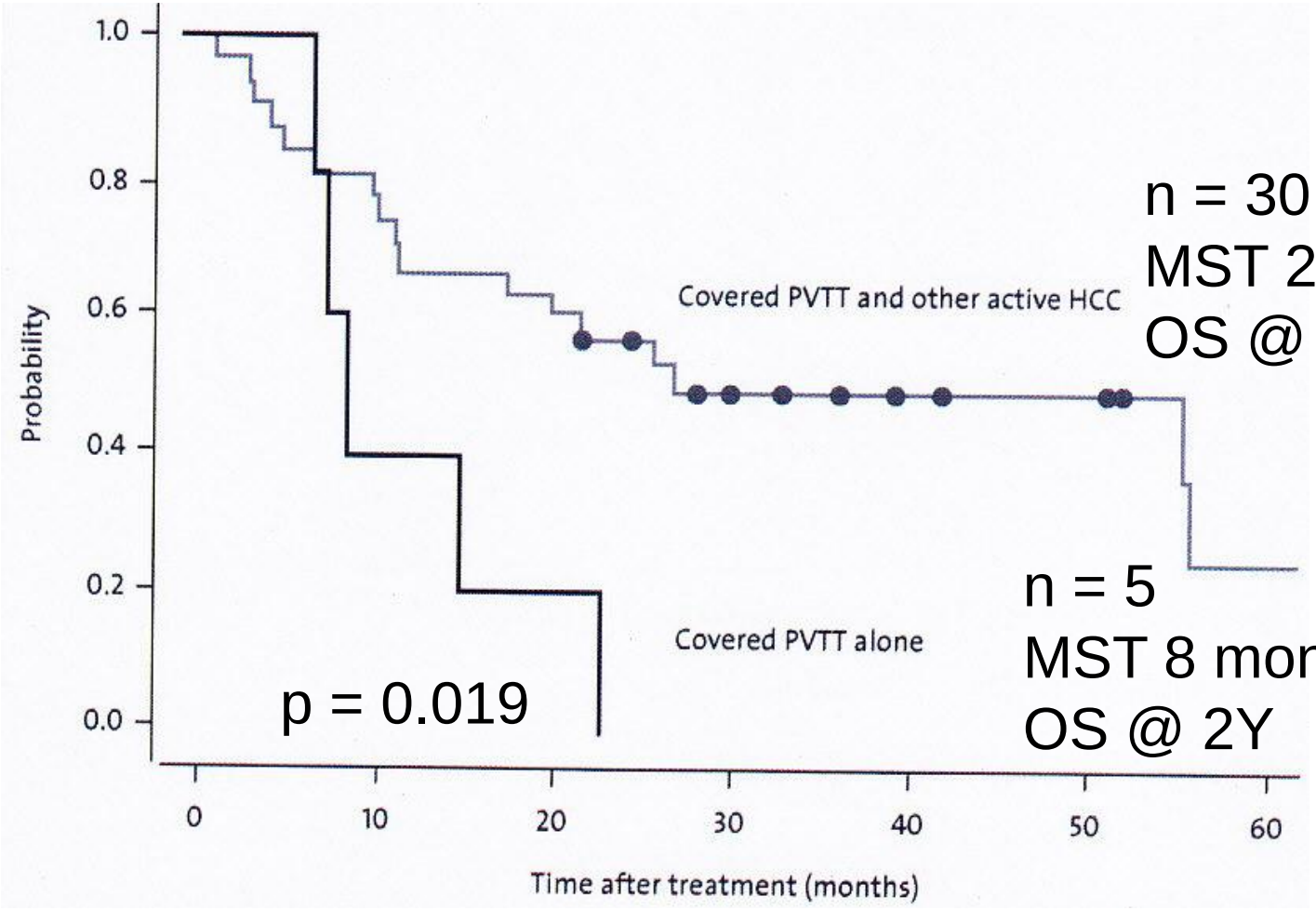
Overall survival in patients treated for PVTT and other active HCC foci vs. those for whom PBT covered PVTT only



n = 30
MST 26 months
OS @ 2Y 57%

n = 5
MST 8 months
OS @ 2Y 0%

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Radiation Therapy for PVTT

Author	No.Case	PVTT	treatment method	RR*	MST(Mo.)	
Tazawa J	24	Vp3,4	TACE+RT50Gy	50	CR,PR;9.7 NC,PD;3.8	2001
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Lin CS	43	Vp3,4	RT45Gy/15fr:22	75	6.0	2006
			3DCRT45Gy/25fr:21	83	6.7	
Tsukuba	35	Vp3,4	PBT 72.6GyE (55-77)	91	22	2009

*RR: response rate

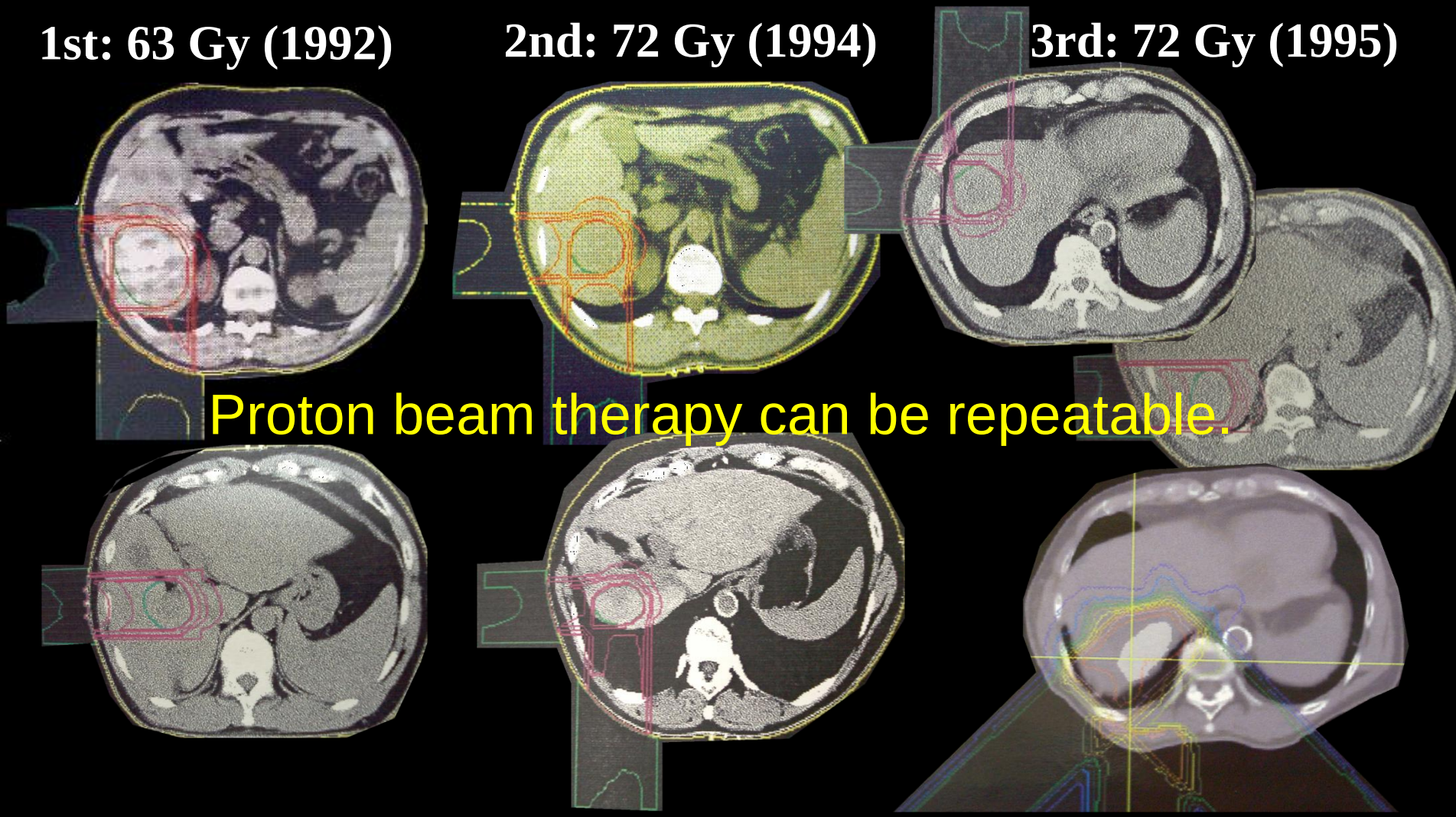
Requirements for the treatment of HCC

- Because of underlying liver dysfunction and multicentric progression

- **High local control rate**
- **To save functioning liver volume as much as possible**
- **Repeatable for newly developing lesions**

Case: a 47 year old woman with chronic hepatitis (B) and aplastic anemia

1st: 63 Gy (1992) **2nd: 72 Gy (1994)** **3rd: 72 Gy (1995)**



Proton beam therapy can be repeatable.

4th: 70 Gy (1998) **5th: 72 Gy (1999)** **6th: 60 Gy (2002)**

Summary

- Precise tumor localization and management of respiratory movement are crucial for treatment of intrahepatic tumor.
- Proton beam therapy offers good local control regardless of tumor location .
- Countermeasures for intrahepatic recurrence and distant metastases are quite important in view of long-term survival.

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