The Role of Radiation Therapy for Hepatocellular Carcinoma

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Anatomic and Physiologic Considerations

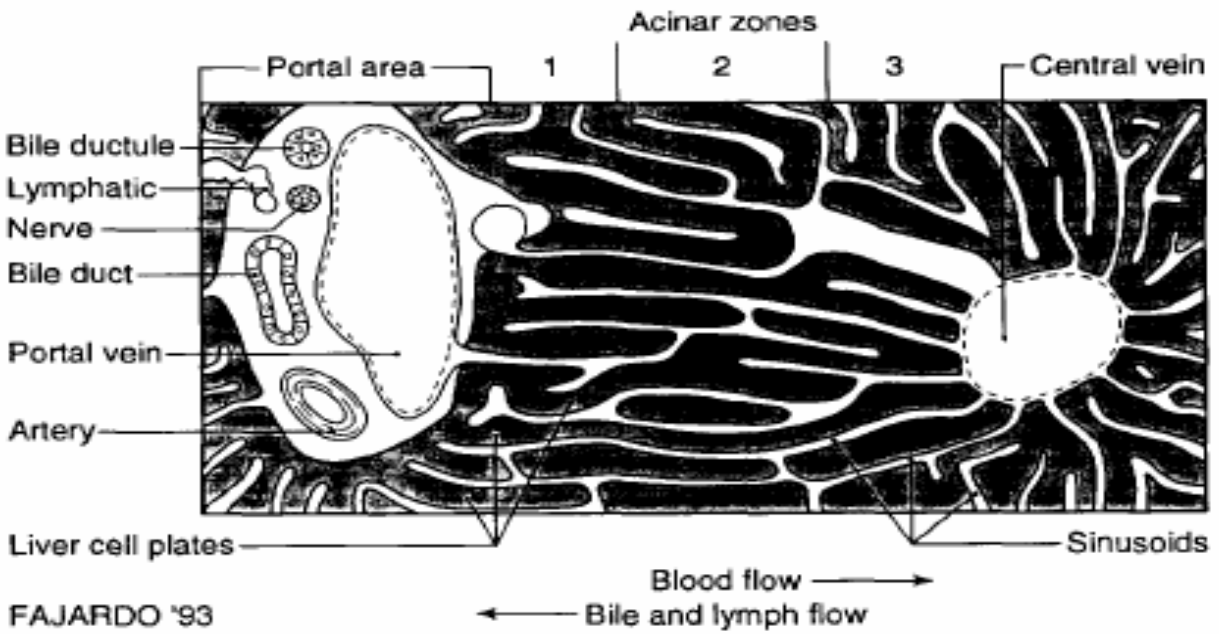


Fig. 1. Normal anatomy of a human hepatic lobule. This diagram depicts a radial segment of a lobule, the center of which is the central vein shown to the right. The periphery corresponds to the portal area in the left. The plates of liver cells are indicated in dark gray, and the sinusoids that run from the portal vein to the central vein are the white spaces between liver cell plates. The acinar zones 1, 2, and 3 divide the parenchyma of the lobule into concentrical regions. The endothelial lining of sinusoids is shown in Fig. 2.

Anatomic and Physiologic Considerations

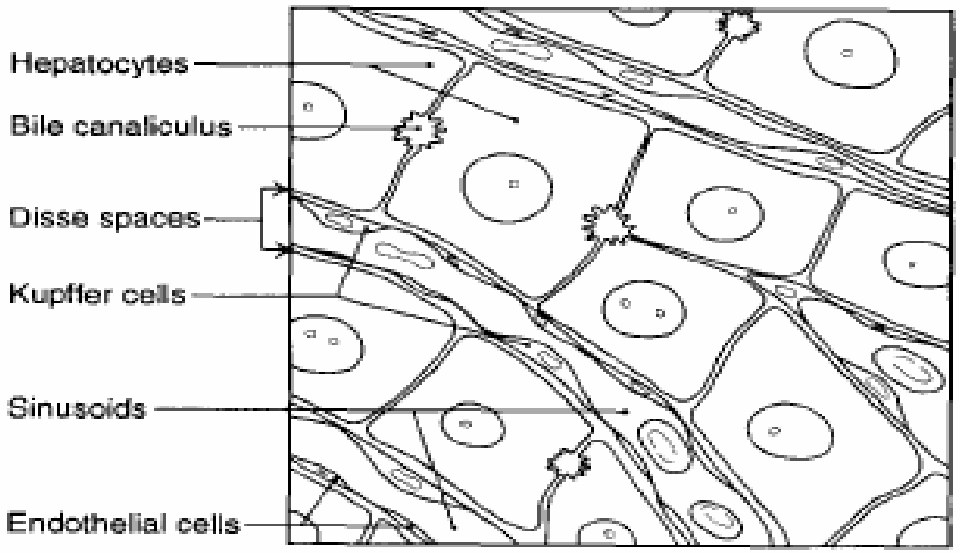


Fig. 2. Detail of normal liver parenchyma at high magnification. The cuboidal hepatocytes form anastomosing plates separated from each other by sinusoids. The latter are lined by endothelial cells interspaced among which are Kupffer cells. The bile canaliculi are spaces delimited by the liver cells' plasma membrane, which forms microvilli. Between the liver cells and the endothelium (which does not have a basement membrane) is the narrow Disse space.

Tolerance of Liver to Radiation

- Liver is a relatively radiosensitive organ
- The major sensitive part is the small blood vessels which show sinusoidal congestion, hyperemia, loss of central hepatic cells and endothelium. Later on fatty vacuolization, fibrosis and atrophy change.
- Hepatocytes are relatively radioresistance. They are in low mitosis rate.
- Usually, radiation response can be observed on 2-6 weeks after complement of the irradiation.

Pathophysiology

- Common pathological lesion associated with the clinical syndromes of RILD (Radiation Induced Liver Disease)
  - "VOD" Veno-occlusive disease
    - Areas of marked congestion which involve chiefly the central portion of each lobule.
    - Foci of yellow necrosis.
    - If the lesion involves large areas of the liver such as an entire lobe, it may produce marked decrease in size with a wrinkled or granular capsule.

The tolerance of radiation:

	1/3 Volume	2/3 volume	Whole organ
Liver	50	35	30
Kidney	50	30	23
Bowels	50		40
Spinal cord	50	50	47
Lungs	45	30	18

Unit: Gy

The Salvage Treatment for Hepatocellular Carcinoma with Portal Vein Thrombosis by 3-Dimensional Conformal Radiation Therapy

Introduction (I)

- Hepatocellular carcinoma (HCC) is the leading cause of death for the malignant neoplasm in Taiwan.
- Less than 15% of the cases have the indications for surgical treatment at the initial diagnoses for HCC.
- The rest of the cases are gone for trans-arterial embolization (TAE) or percutaneous ethanol injection (PEI).
- However, in the situation of HCC with portal vein thrombosis, the outcome is extremely poor. The one-year survival is zero for those patients.

Incidence of PVT in Hepatoma Patients

- Sarrat et al (USA) 23 %
- Edmondson et al (USA) 33.8 %
- Nakashima et al (Japan) 64 %
- Lai et al (Taiwan, NTUH) 62.5 %
- VGH (Taiwan) 56 %
- KMUH (Taiwan) 56.7 %

Incidence of PVT in non-malignant liver disease

- Okuda et al Japan 0.573%
- KMUH Taiwan 0.3%

Chen et al in KMUH

96 non-treated hepatoma patients

	Ave. survive (Days)	6 Months	12 Months	18 Months
29 PVT (-)	206	36%	22%	13%
67 PVT (+)	48	4%	0%	0%

The causing factors for PVT (multiple variant analysis)

- Tumor size (≦5cm, 5~10cm, >10cm)
- AFP (≦20, 20~40cm, >400)
- Single, multiple and diffuse

Introduction (II)

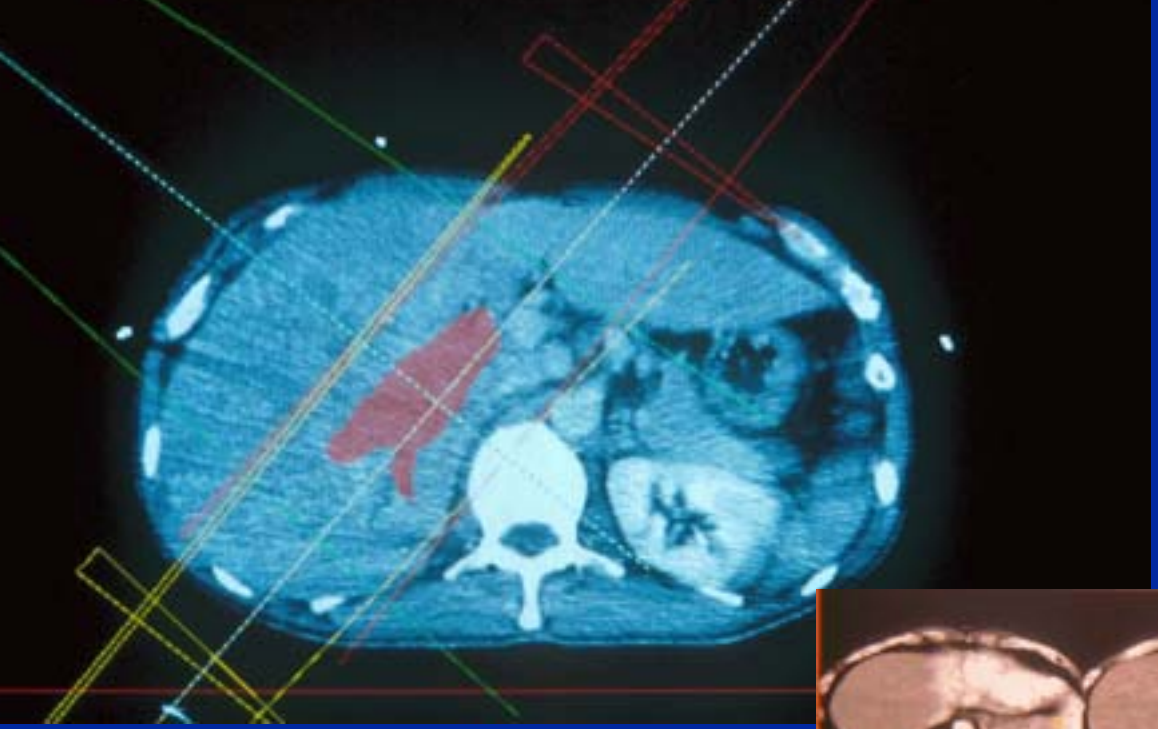
- The innovation technique of 3-dimensional conformal radiation therapy (3D-CRT) has been used for irradiating the occlusion part of portal vein in order to get the patent of venous blood flow. Later on, TAE can be done for these patients.
- 3D-CRT can treat the occlusion part of portal vein or inferior vena cava with the conforming technique in order to avoid the large amount of normal liver tissue inside the irradiated field.

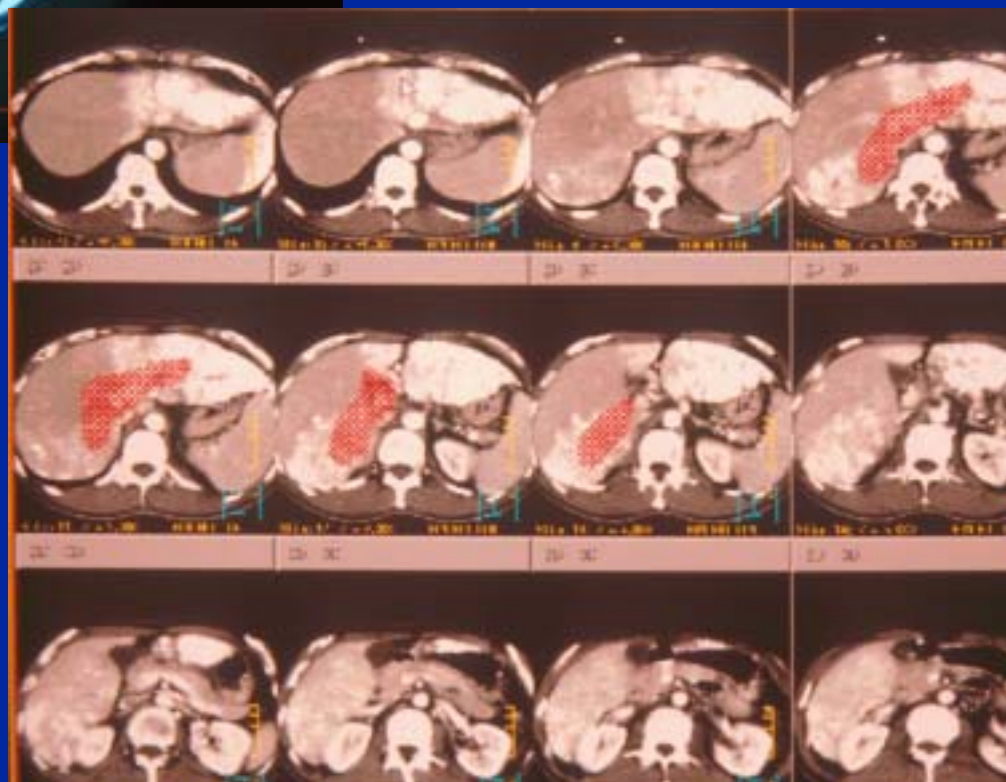
Introduction (III)

- The rule of thumb for liver irradiation
  - Whole liver---------- 25-30 Gy
  - Half liver---------- 40-45 Gy
  - One third of liver----- 50-60 Gy
  - # 10 to 20% dose cut down for the cirrhotic liver and diffused HCC

Materials and Methods (I)

- Treatment planning system: ADAC Pinnacle
- Varian 2100C/D Linear Accelerator: 15 MV X-ray
- Multi-leaf collimator for fields shaping
- Protocol dose: 250 cGy/fr, 5500 cGy/ 22 fr within 5 weeks
- Radiation therapy for PV thrombotic area only: usually 1 to 2 cm safe margin
  Radiation therapy for PVT and primary tumor: usually 0.5-1.5 cm safe margin
- 3-5 treatment fields were planned, evaluated by Dose-Volume Histogram





Materials and Methods (II)

- Minimal one year follow-up for 100 patients
- Liver echogram, CT scan or Liver angiography proved PVT or IVC occlusion
- Liver echogram or CT scan was repeated one month after radiation therapy
- Liver function had been checked before, during and after RT
- Post-RT TAE was considered for primary liver tumors if PV flow resumed

Materials and Methods (III)

- Radiation therapy for PVT only: 72
  - Dose: 5500 cGy/22 fr
- Radiation therapy for PVT and arterioportal shunting: 7
  - Dose:5500 cGy/ 22 fr
- Radiation therapy for PVT and primary tumors: 21
  - Dose: 5600-6400 cGy/ 28-30 fr: 16
  - Dose: 5500 cGy/22 fr: 5

Results (I) -- Patient's characteristics

- From February 1997 to January 1999, 100 HCC with portal vein thrombosis (PVT) patients were treated by 3D-CRT
- Median age: 57 y/o (range 33 to 82 y/o)
- M: F=73:27
- Pathology proved for HCC: 56
  - High AFP: 47 (>400)
  - Moderate high AFP: 23 (20-400)
  - Images diagnosis: 11

- One or more times TAE before R/T: 68
- Thrombotic area distributions:
  - Whole PV: 14
  - IVC: 9
  - Right PV: 32
  - Combined: 22
  - Left PV: 26
  - Main PV: 11
- Combined arterioportal shunting: 7
- Ascites (+): 31

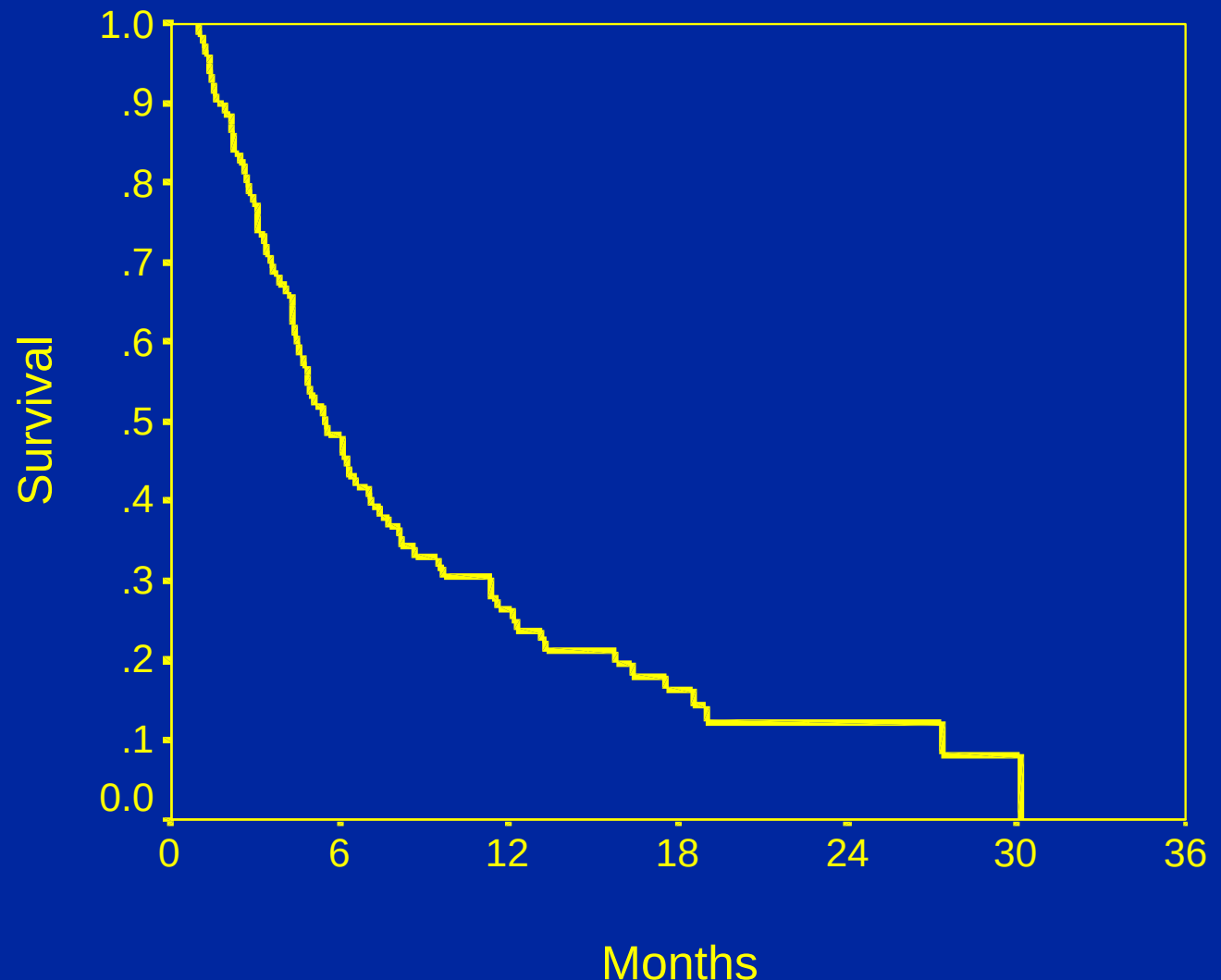
Results (II)

- Portal vein status one month after 3D-CRT
  - Resumed portal flow completely: 31/100 (31%)
  - Resumed portal flow partially: 44/100 (44%)
  - No response: 25/100 (25%)
- Arterioportal shunting disappear: 3/7
- TAE had been performed after 3D-CRT: 42/75 (56%)

Results (III)

- 6 months survival after 3D-CRT:
  - 51/100 (51 %)
- 12 months survival after 3D-CRT:
  - 28/100 (28%)
- 18 months survival after 3D-CRT:
  - 15/100 (15%)

2-year survival of hepatoma patients with PVT treated with conformal radiation therapy



Discussion

- According to the survival report of non-treated HCC patients with PVT from Kaohsiung Medical University, the 6 months survival was 4% and 12 months survival was 0%.
- Salvage treatment with 3-D CRT for HCC with PVT showed 75% resumed rate for portal venous blood flow. Subsequent TAE or PEI can be done to control the progression of the primary tumors.

Discussion

- Prolong survival by the 3D-CRT was also seen for this group of patients.
- Limited side effects with good tolerance for most of the patients received this salvage treatment.

Preliminary Results of 3-Dimensional Conformal Radiotherapy for Hepatocellular Carcinoma with Portal Vein Thrombosis-----Wei-Chung Hsu, Chin J Radiol 2002; 27:59-66

24 HCC patients with PVT were treated with 3D-CRT

Mean age: 54.1 y/o, (range from 30-73 y/o)

Dose: 1.8-2 Gy/ fr, total dose range from 43.2- 75 Gy)

Results: response rate:63% (15/24)

6 months survival rate:72 %

1 year survival rate:55.4%

#Cox's regression model analyzed the factors affecting the prognosis

Treatment dose, Treatment volume

Intrahepatic or extrahepatic involvement

The British Journal of Radiology, 73 (2000), 550–552

Case report

Conformal radiation therapy for hepatoma with portal vein thrombosis

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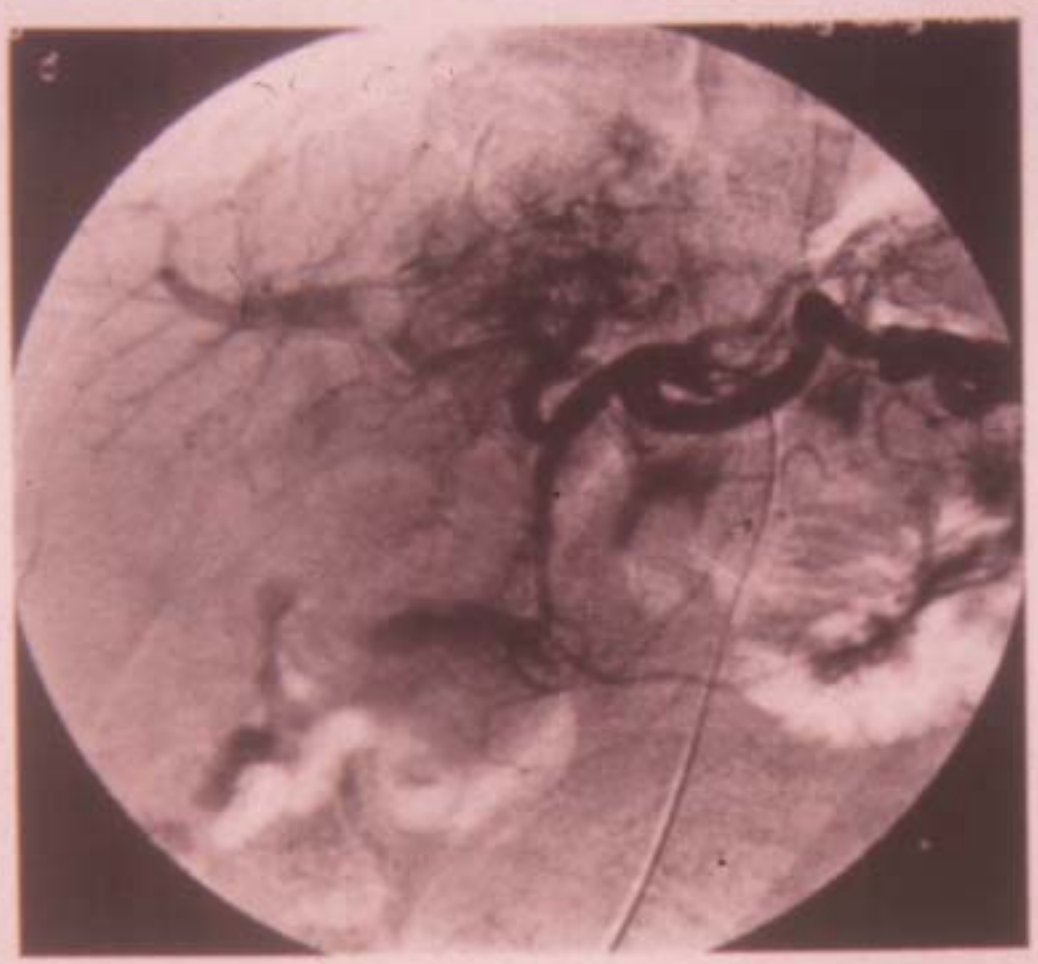


Figure 1. Coeliac angiography before radiotherapy showing hypervascular tumours with tumour vessels and marked contrast in the tumour of the left lobe of the liver. Abnormal hepatic arterioportal shunting is noted in the early arterial phase. Tumour thrombus inside the right portal vein is also seen.

Figure 3. Coeliac angiography 4 weeks after radiotherapy shows absence of the tumour vessels and contrast in the left lobe of the liver. No arterioportal shunting is found.

Clinical Syndromes – Subacute RILD

- RILD typically occurs 4-8 weeks after the completion of treatment, although it had been described as early as 2 weeks and as late as 7 months.
- Rarely jaundiced at presentation.
- Physical examination reveals ascites and hepatomegaly in moderate to severe cases.
- Serum chemistries tend to show moderate elevations of AST and ALT. (In the range of two-fold above normal).
- Minimal or no increase in bilirubin.
- Substantial rise in alkaline phosphatase (in the range of 3-10 times above normal)

Innovation R/T Technique for Liver Treatment

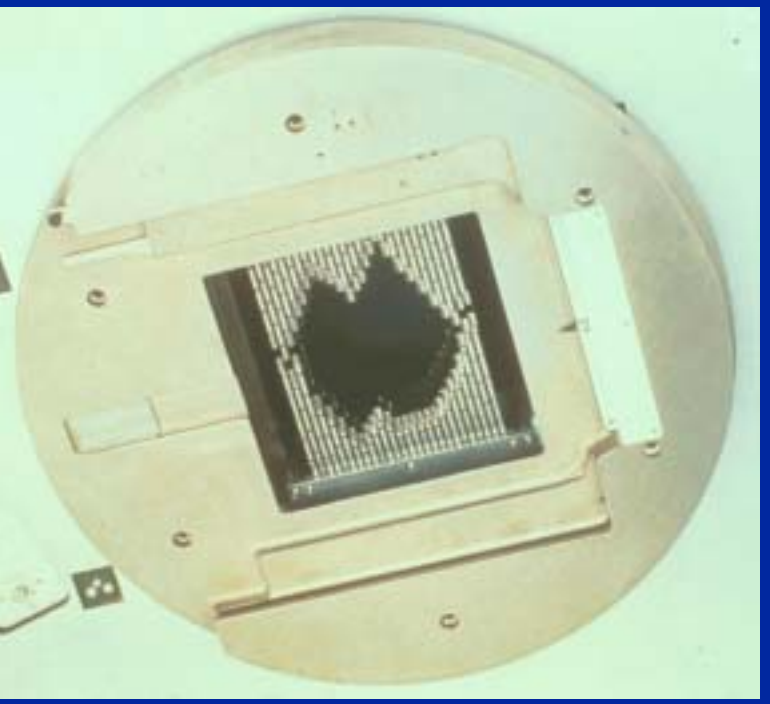
- Conformal Radiotherapy
- Intensity Modulation Radiotherapy
- Ultrasound Guide Radiotherapy
- Active Breathing Control

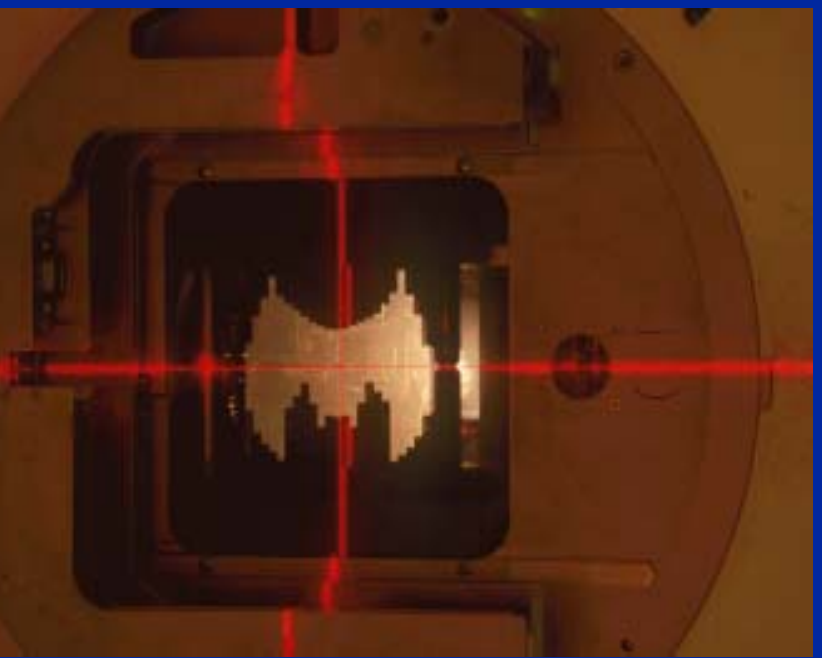
Three Dimensional Conformal Radiotherapy

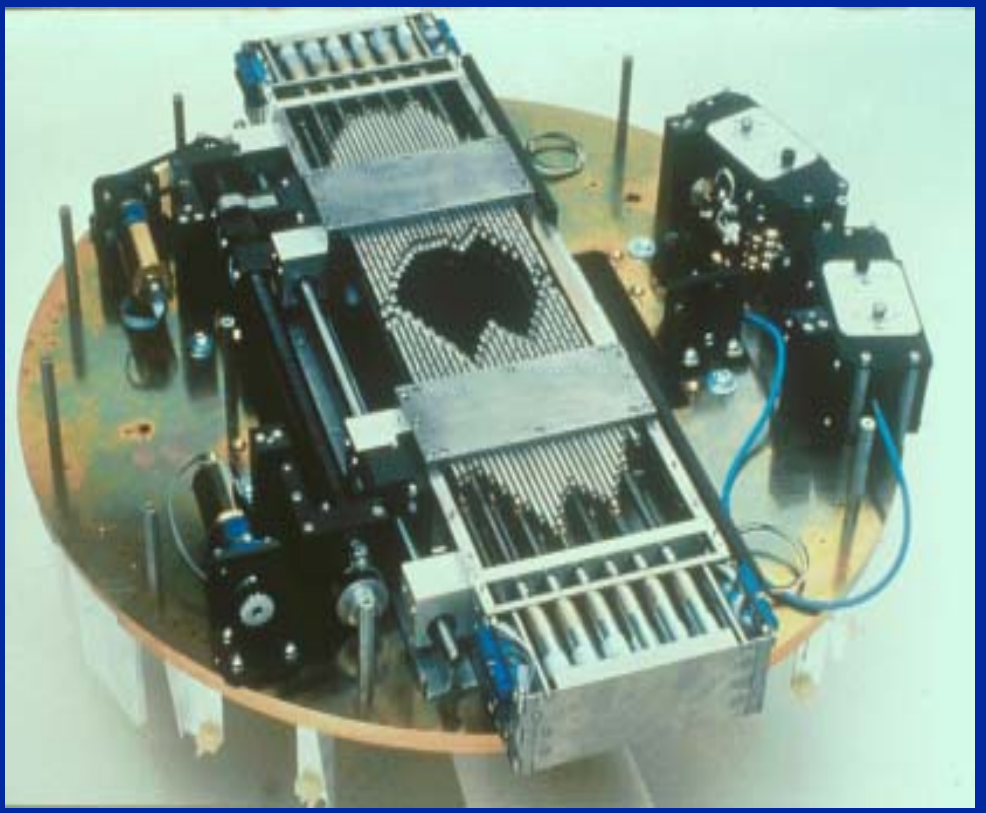
三度空間順形放射治療

其藉由精密的電腦硬體及軟體設備，順著腫瘤形狀設計出治療照野，能有效阻擋正常組織接受過高之劑量，降低副作用的產生，並進一步提高腫瘤劑量，增加局部控制率。


Precise

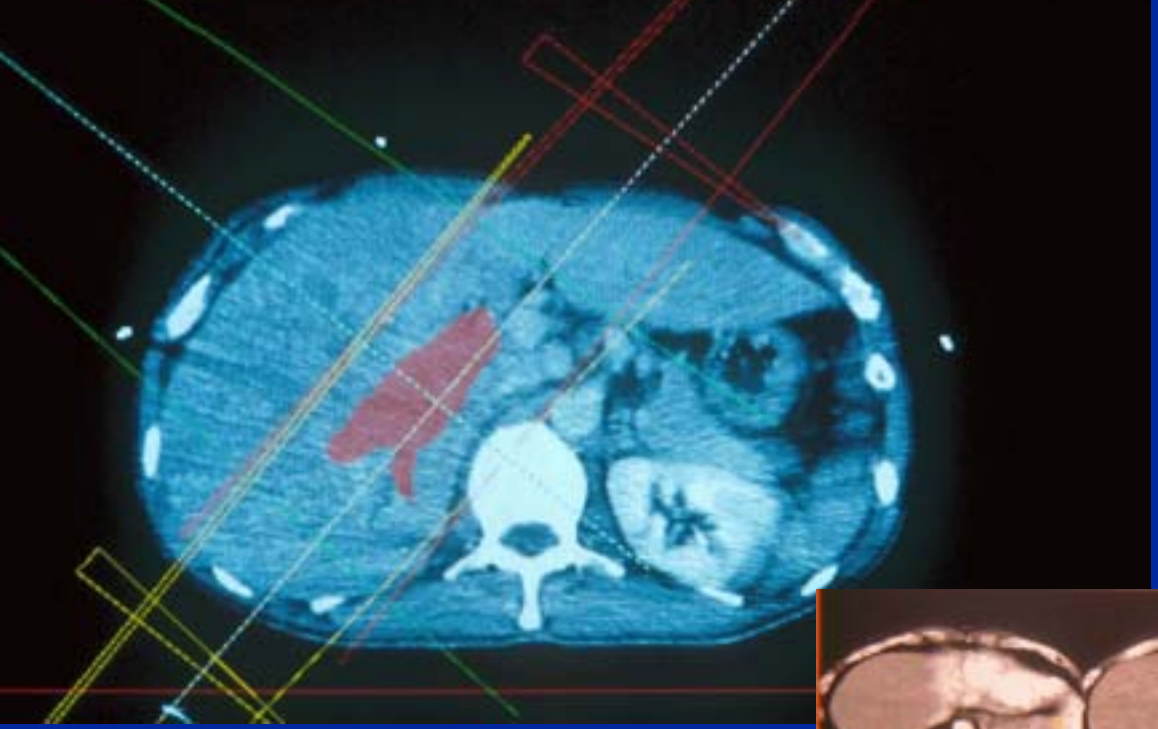


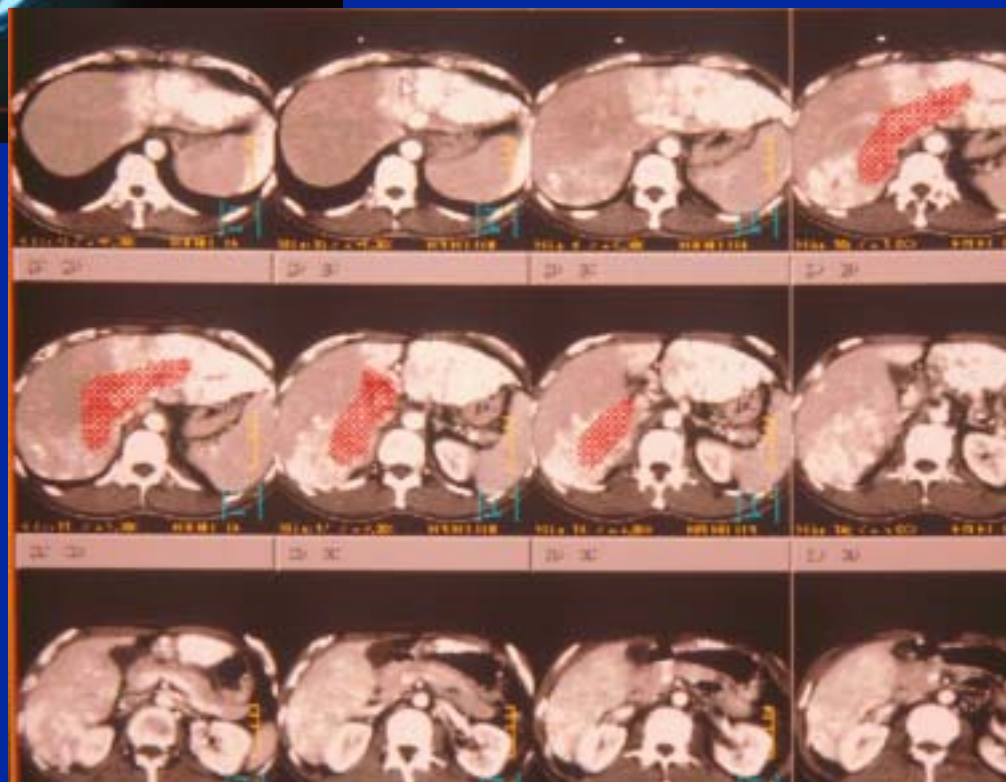


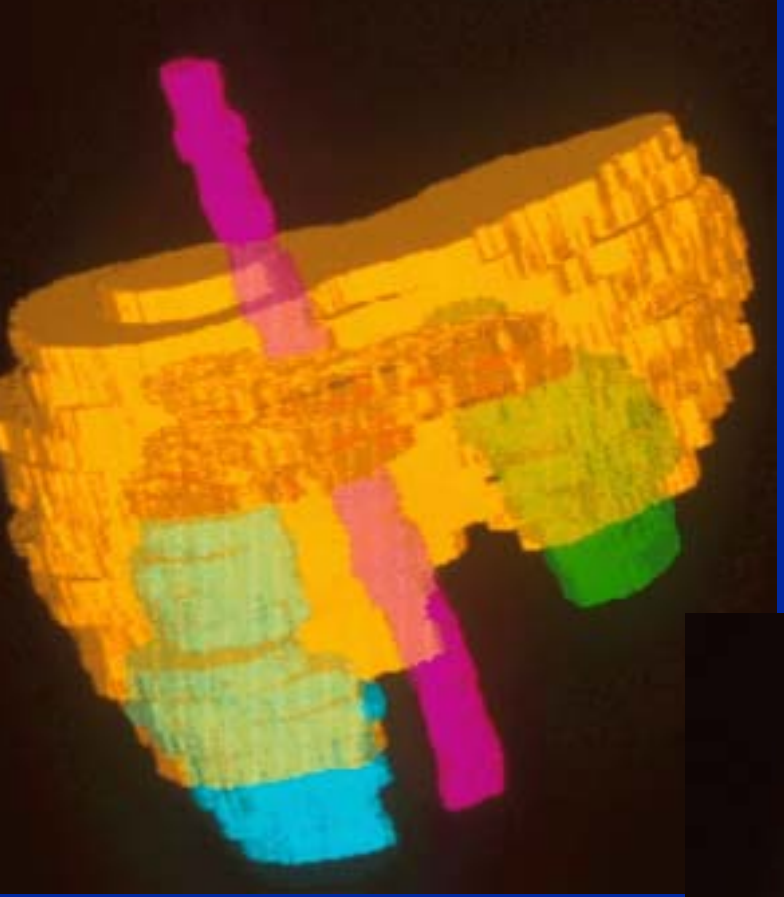


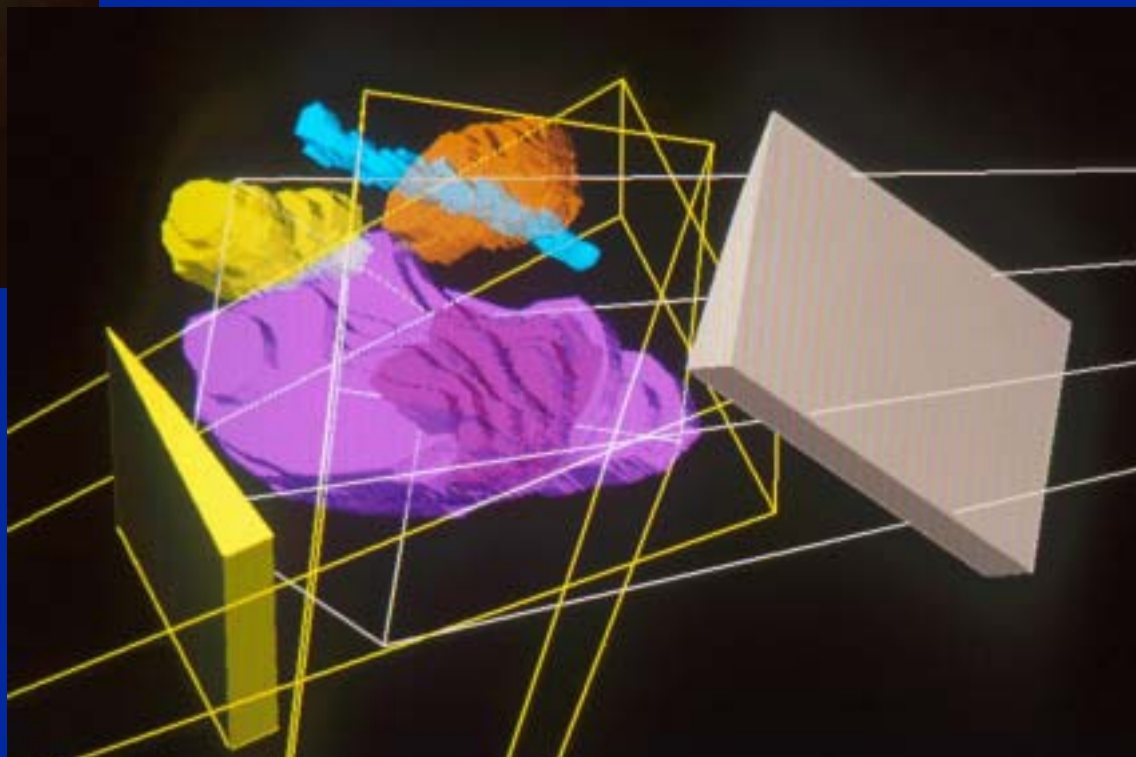
Multi-Leaf Collimator(MLC)

多葉式準直儀







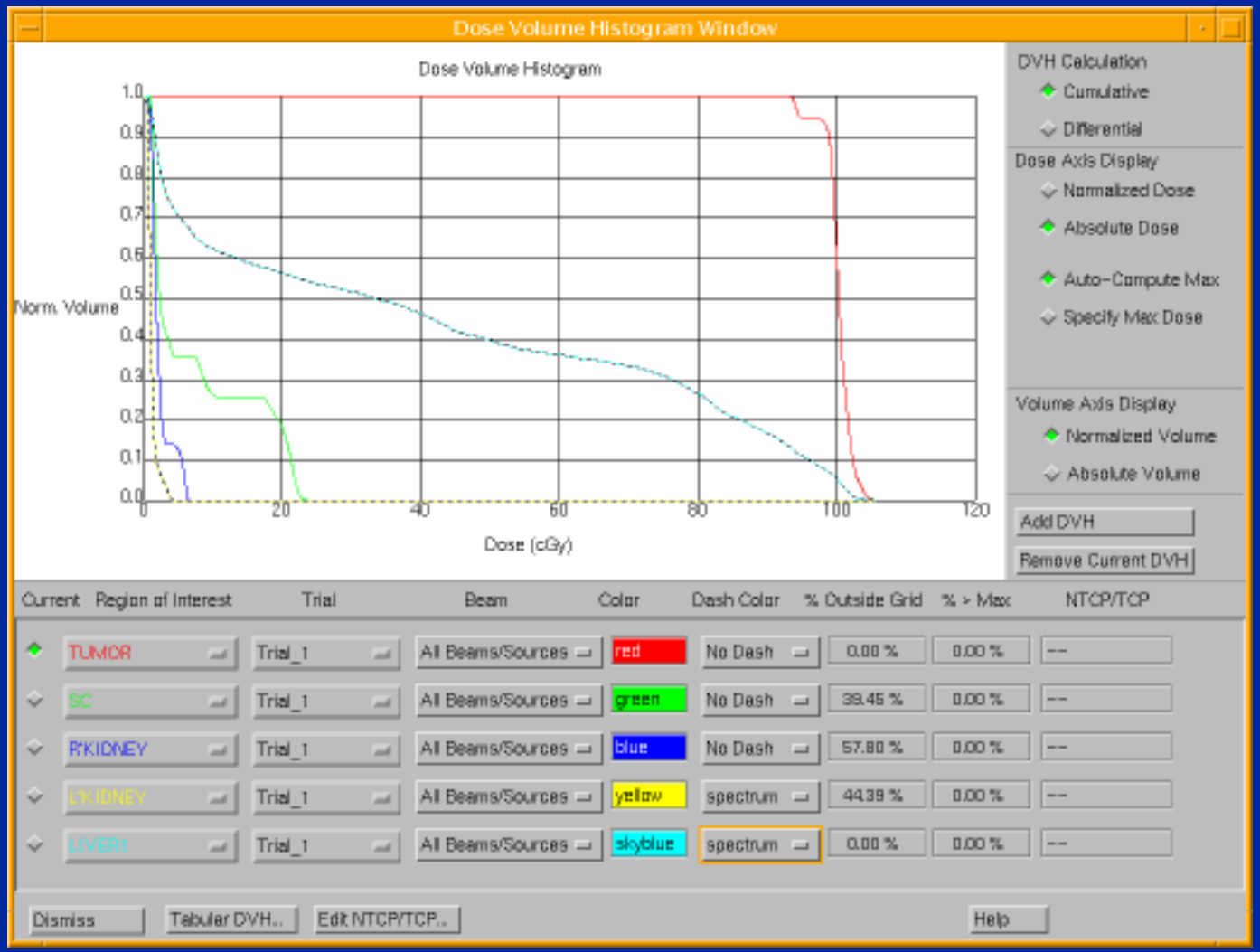


Treatment Planning

Dose-Volume Histogram:

is used to describe the integral volume of the target and specific normal organs at a function of dose

Dose Volume Histogram



The tolerance of radiation:

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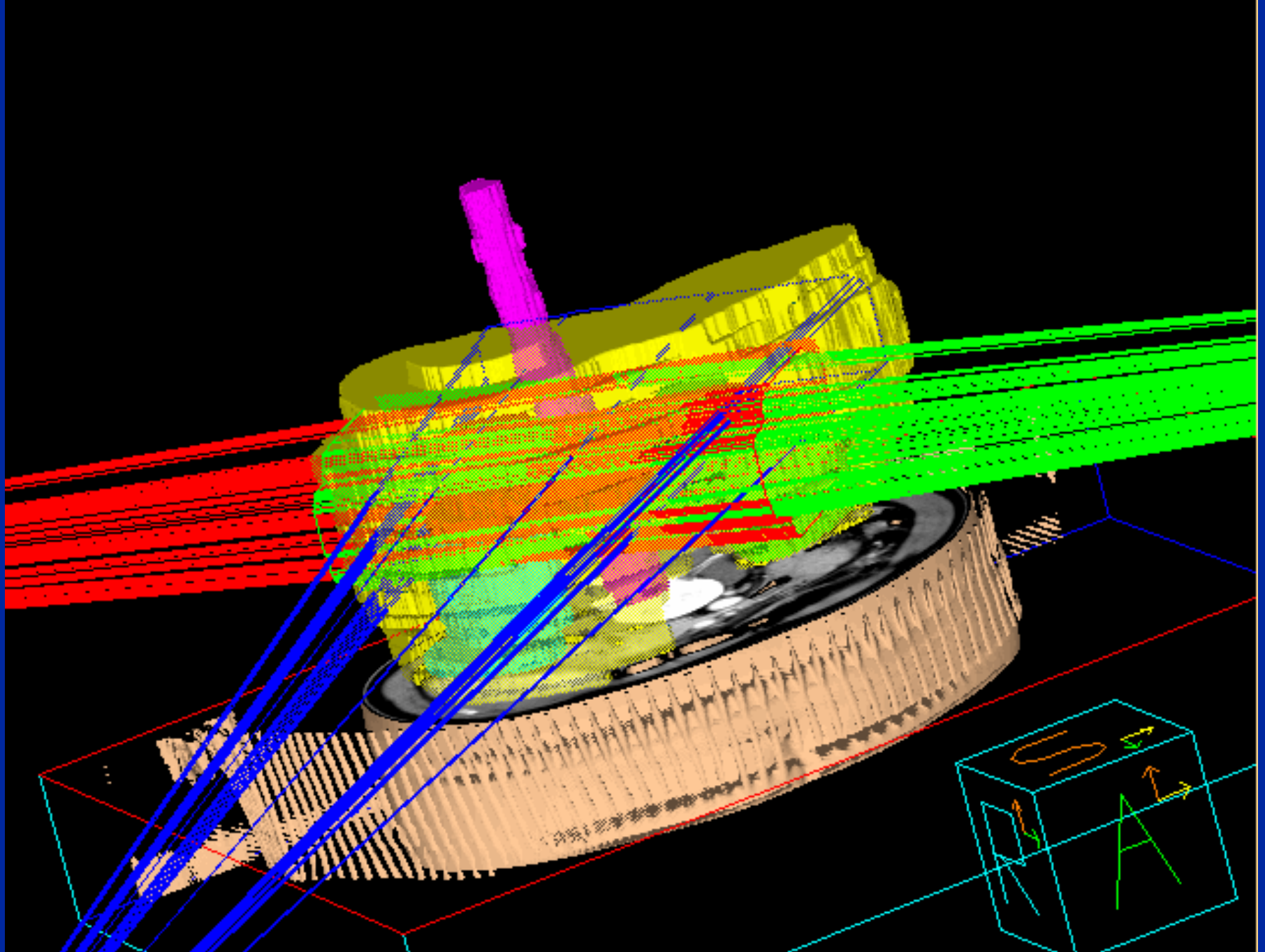
Unit: Gy

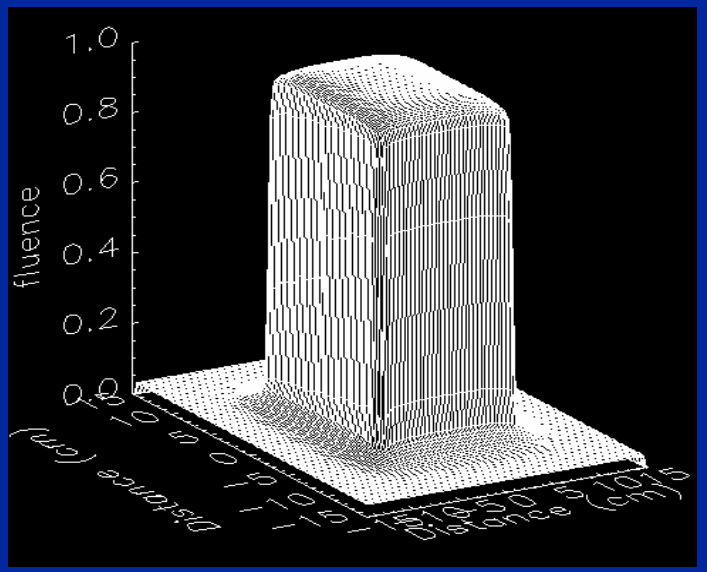


Intensity Modulation Radiation Therapy

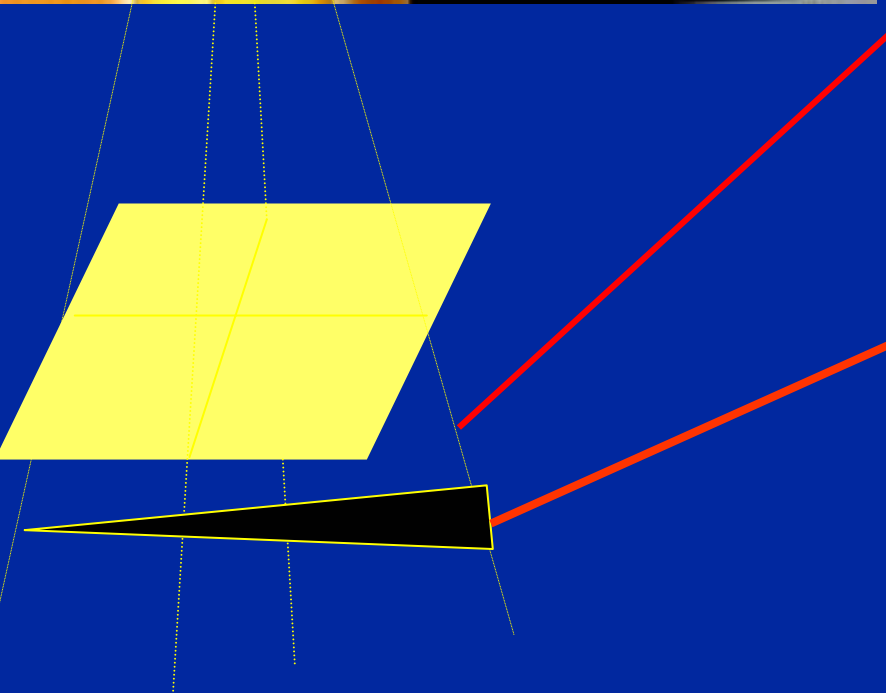
IMRT

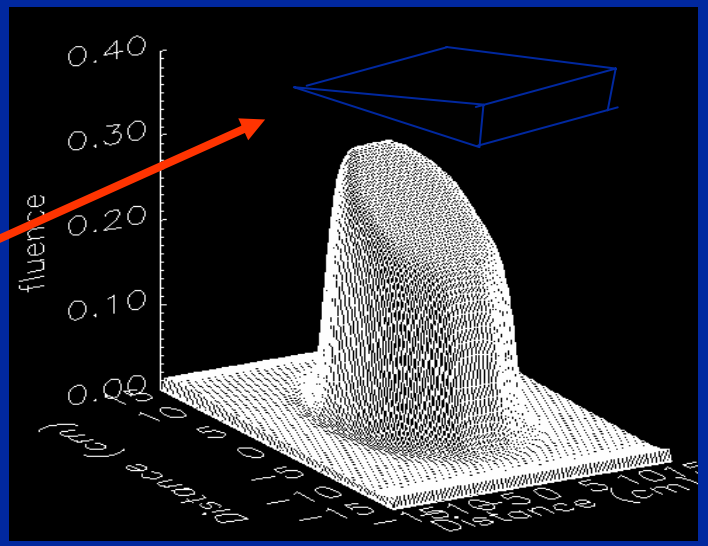
強度調控放射治療

- IMRT是一種最先進的放射治療技術，可多方向照射，並由電腦調控射線強度，使腫瘤接受較高劑量，減少正常組織的輻射傷害。



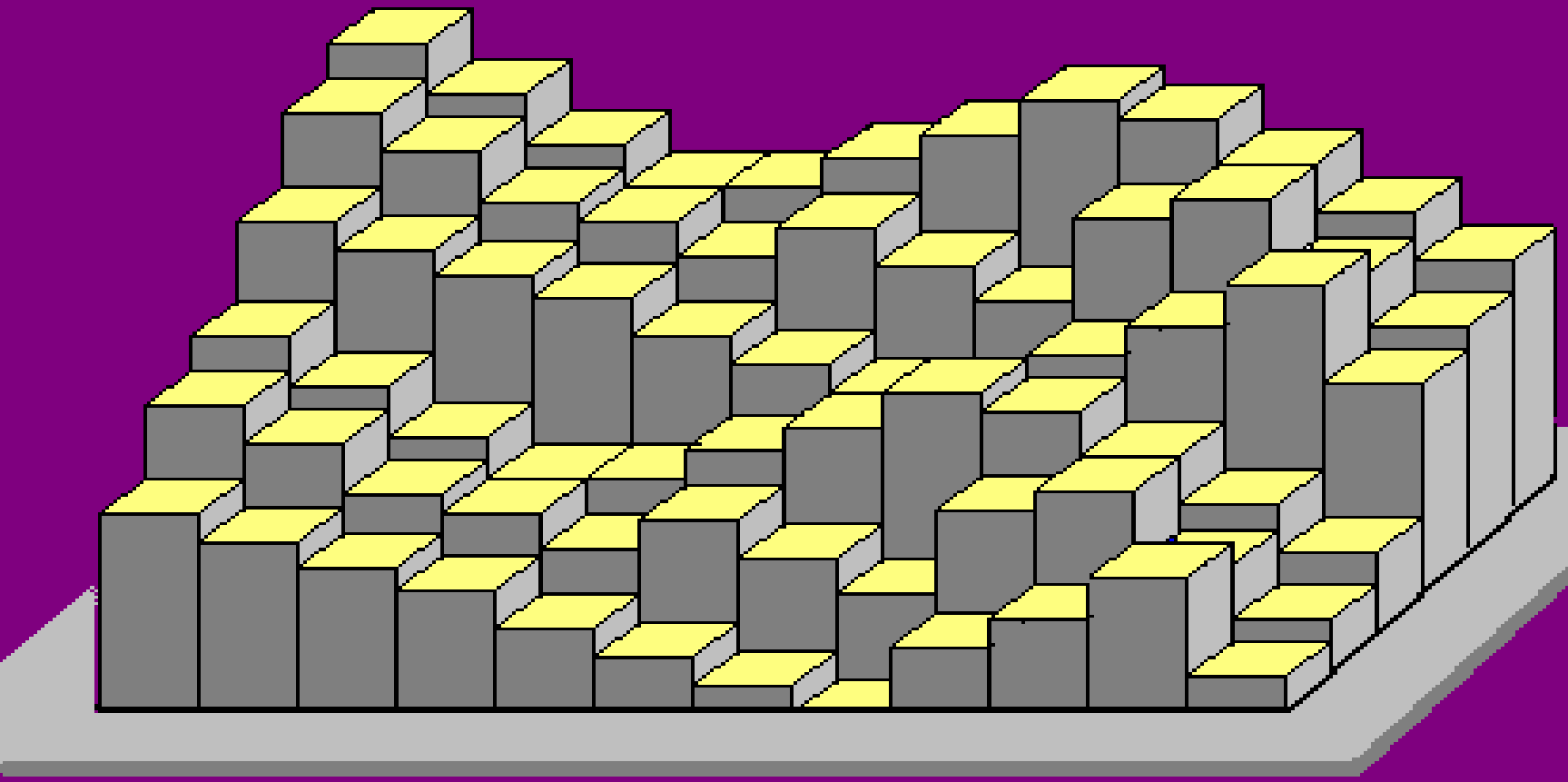
Open field





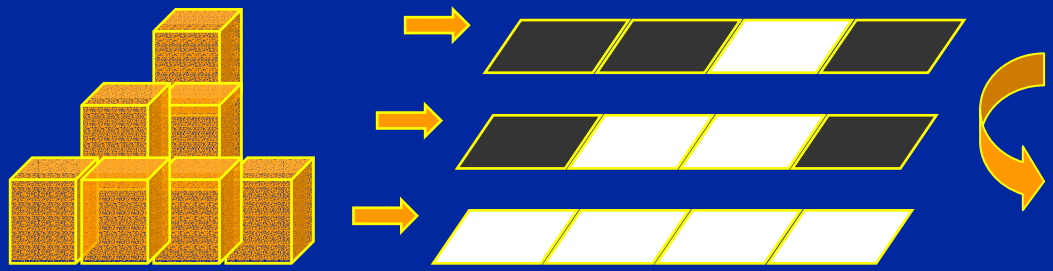
With wedge field

3-D Tissue compensator:



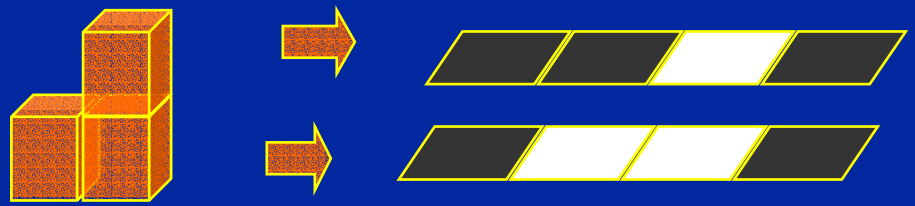
Classic, 3-D, manual tissue compensator

MLC

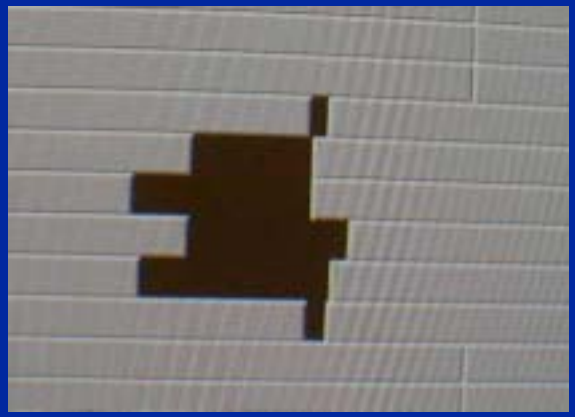


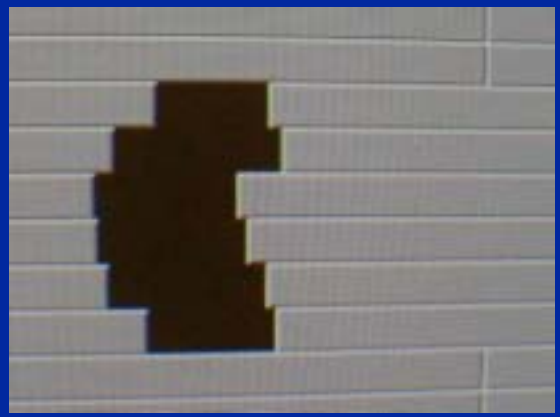
Leaf pair #1

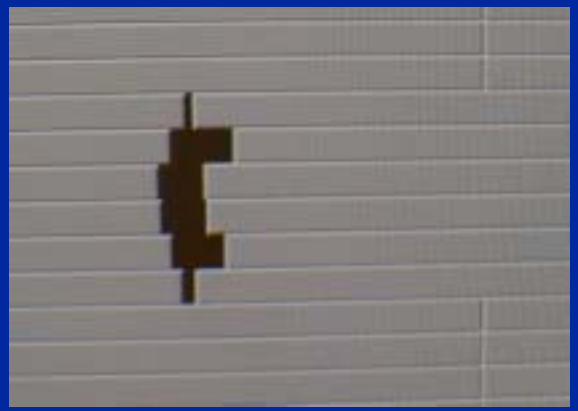
Step by step

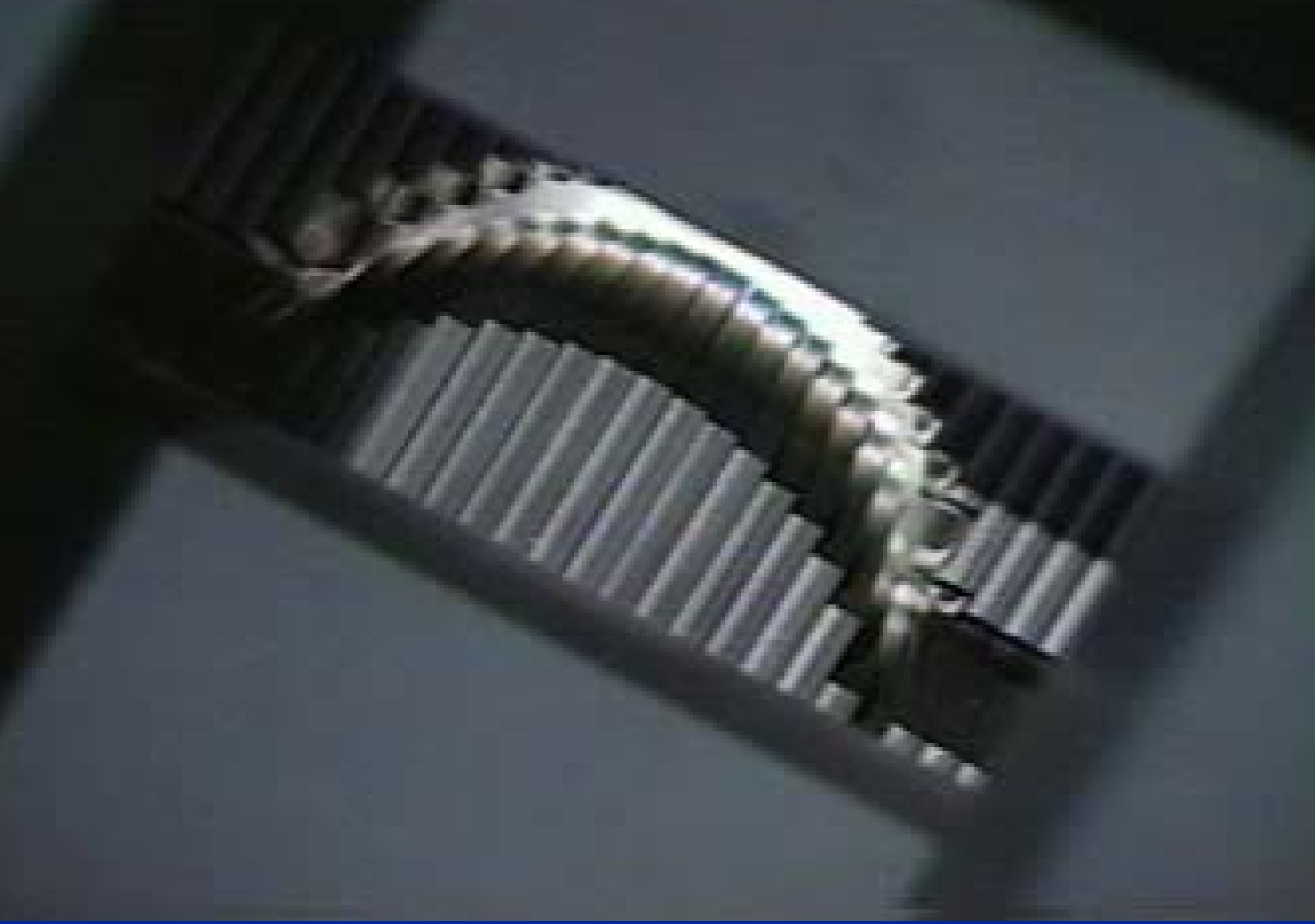


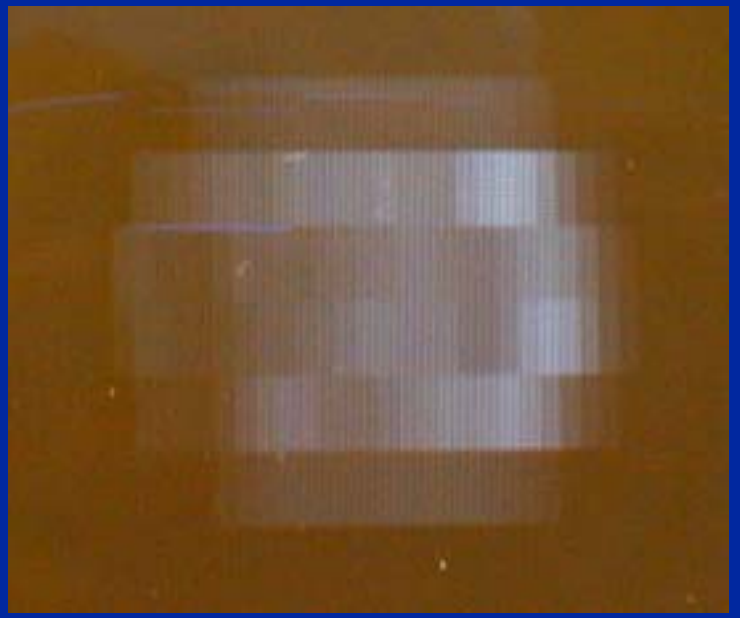
Leaf pair #2

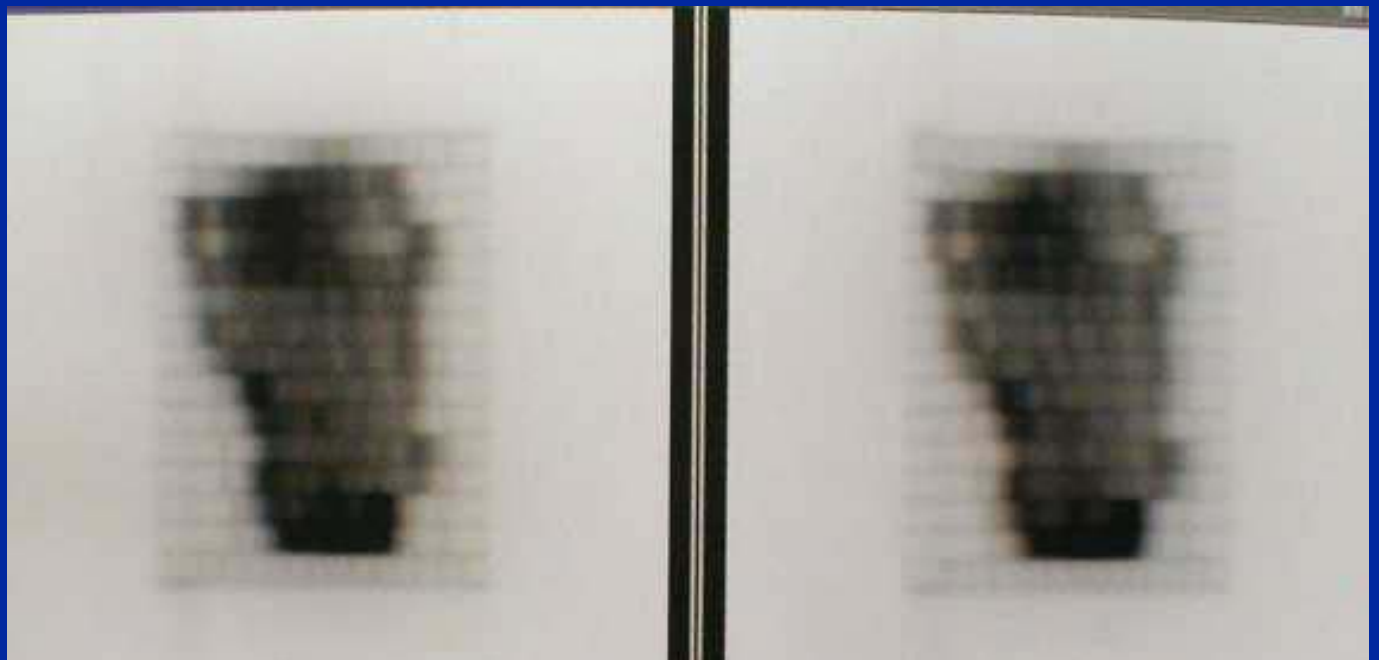












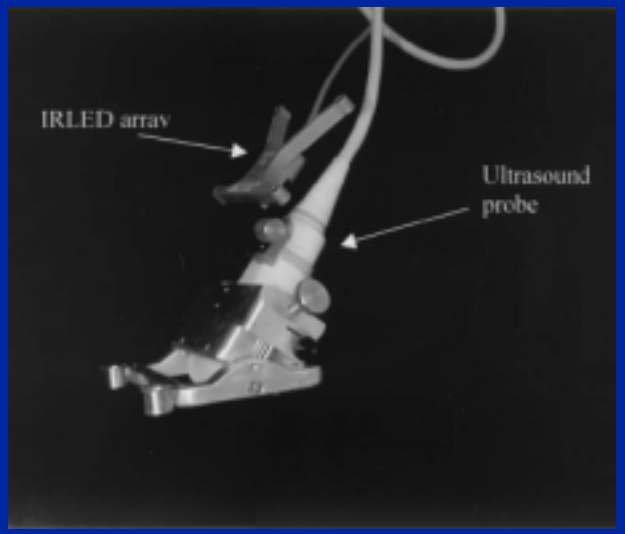
Ultrasound guided Radiotherapy

Optically Guided Ultrasound for Extracrainal Radiosurgery System Description

- 3D ultrasound guidance
- Inexpensive
- Flexible
- High resolution imaging modality
- Real time

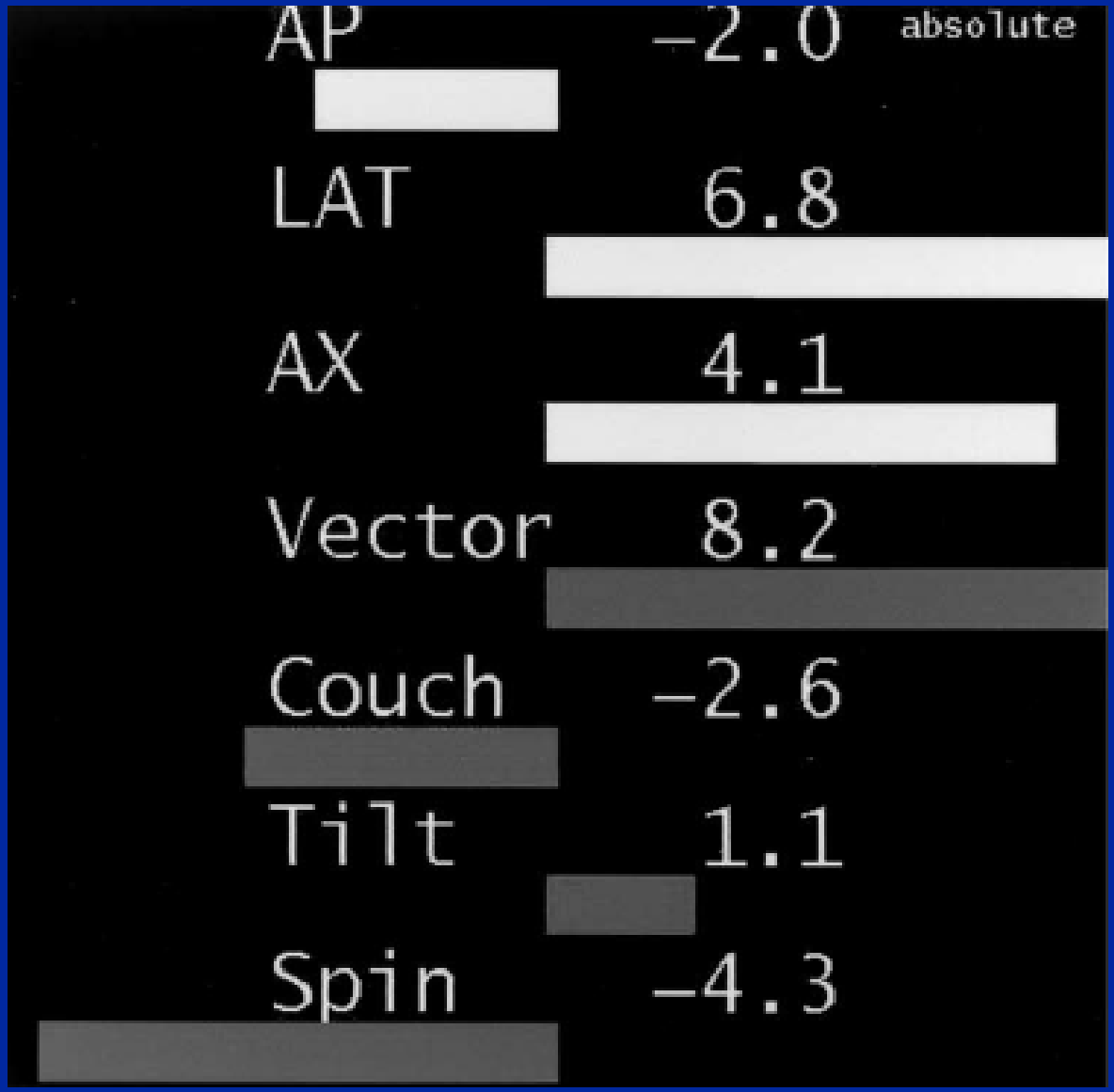
Optically Guided Ultrasound for Extracrainal Radiosurgery System Description

- To generate 3D ultrasound data sets through optical tracking of free-hand acquired 2D ultrasound data
- 2D data are transferred to a computer workstation using a standard video link
- 4 infrared light-emitting diodes (IRLEDs) attached to the probe for determined the orientation of the probe
- CCD cameras are used to determine the positions of the IRLEDs
- Ultrasound pixel and volume can be determined and reconstructed.


IRLED array
Ultrasound probe

Optically Guided Ultrasound for Extracrainal Radiosurgery System Description

- The probe position coordinate system at the time of data acquisition is sufficient to determine the position of the image volume relative to the linac isocenter.
- The determination of the relative position of the image and probe corresponds to a calibration step that is performed at the time of system installation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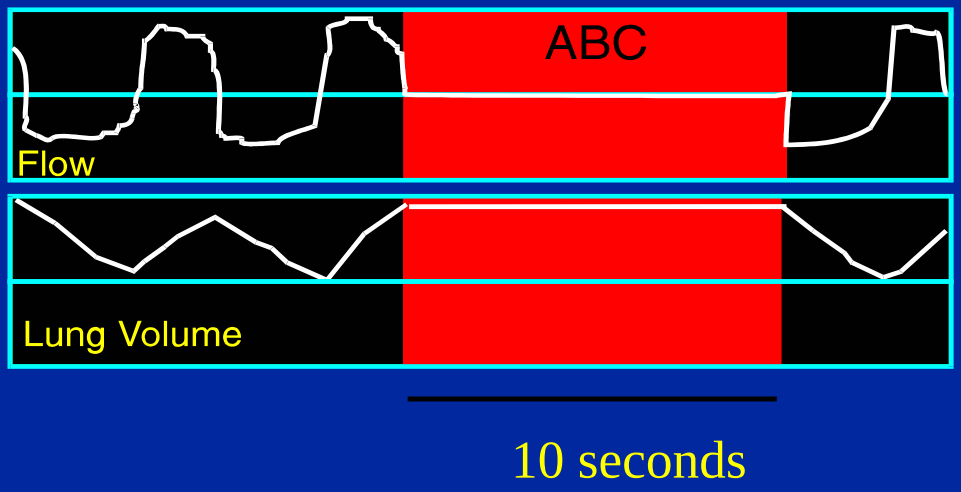
Active Breathing Control (ABC)



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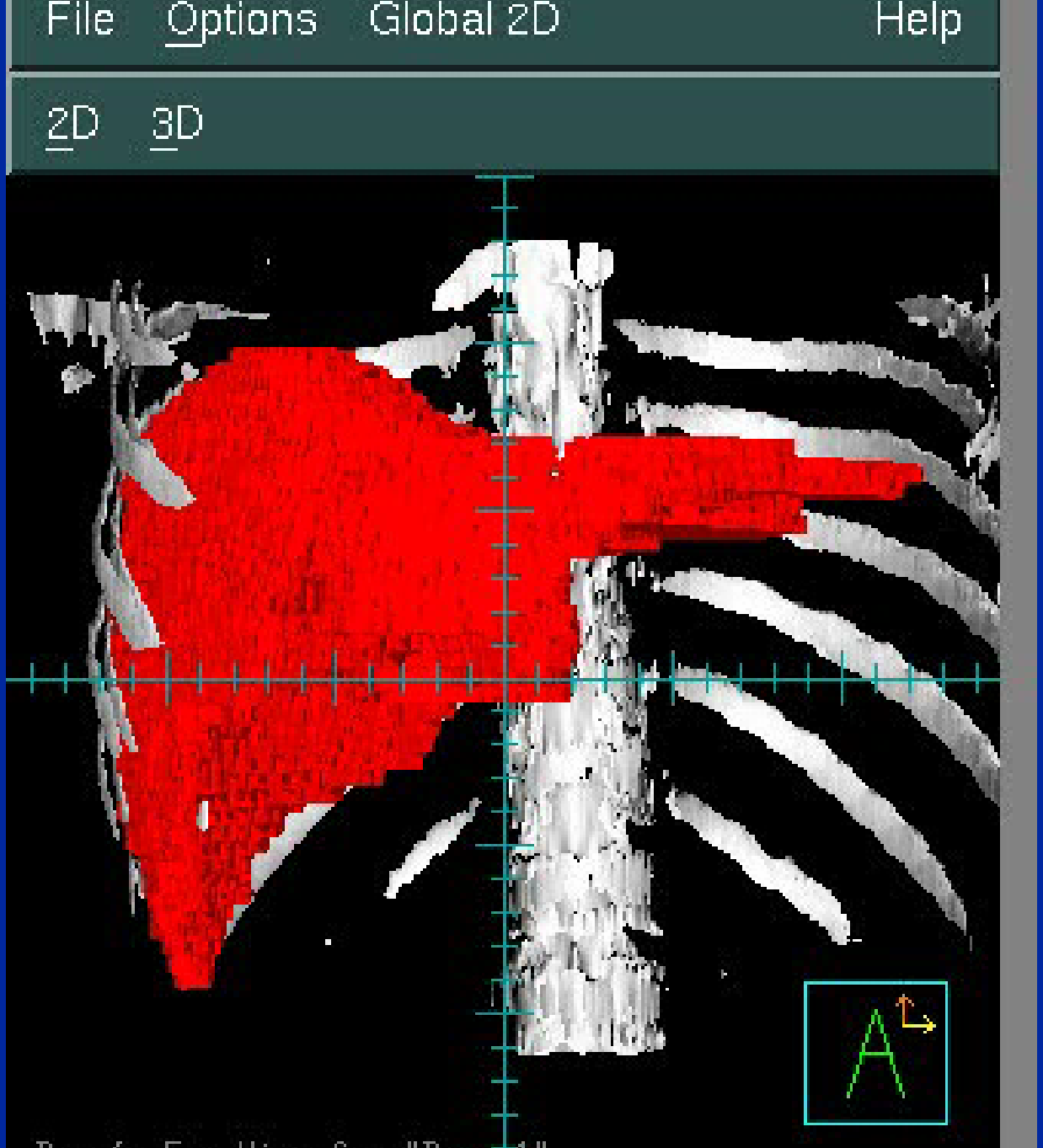
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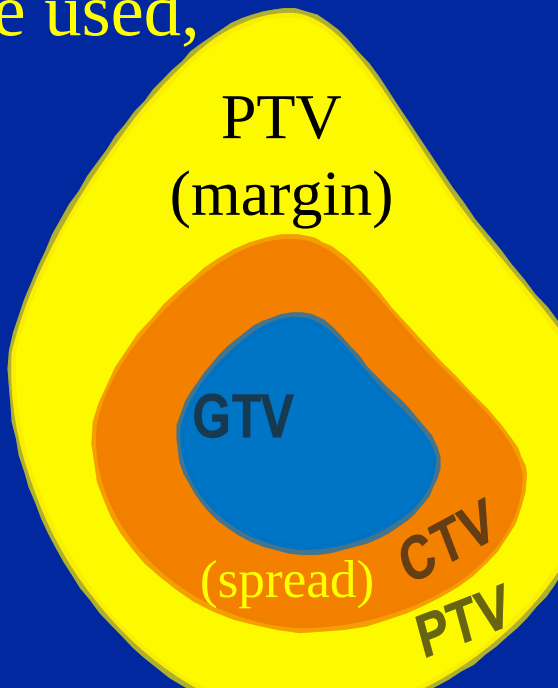
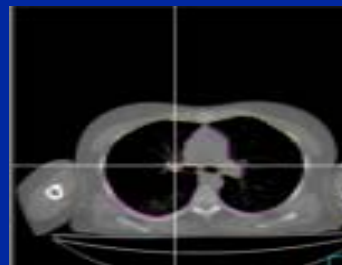
Uncertainty from Breathing Motion

- Clinical Need:
  - Organs and tumours in the thorax and abdomen are known to move by more than 2 cm during the breathing cycle.
  - Wide treatment margins are therefore used, irradiating a large volume of critical tissue, and inevitably limiting the dose that can be delivered to the tumor.

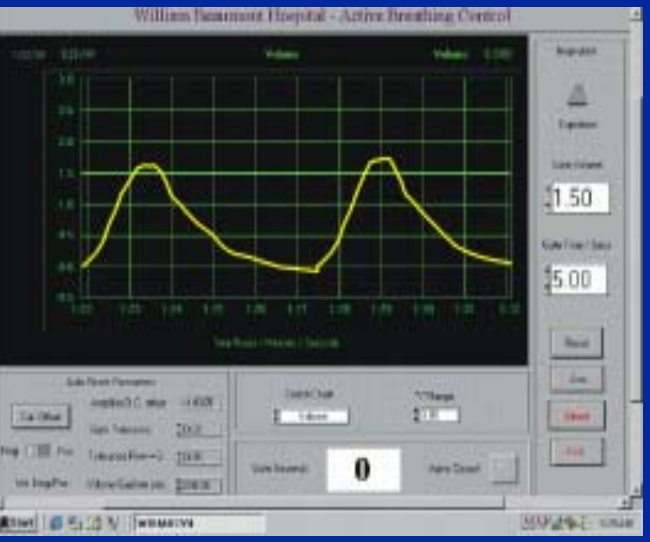


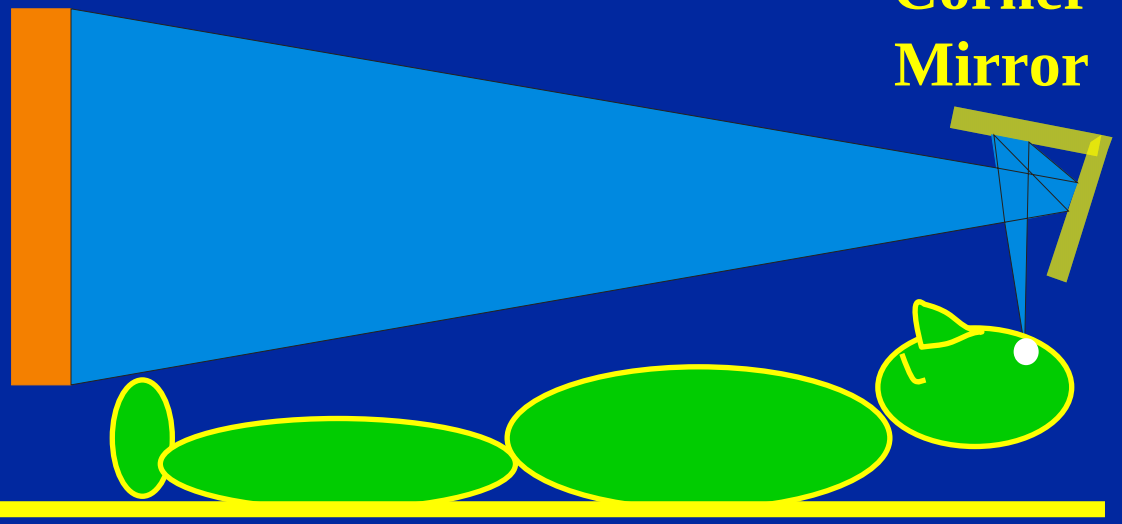
Uncertainty from Breathing Motion

- Margins accommodate organ movement caused by breathing and assure target coverage, but irradiate more normal tissue.
- Breathing motion is a potential obstacle to the use of IMRT for disease in the thorax and abdomen.
- Other strategies for dealing with breathing motion:
  - Treatment beam on/off with respiratory signal (gating).
  - Voluntary, deep inspiration breath-hold (DIBH)
    - Unpredictable. Same for CT as for treatment?
  - Active breathing control (ABC).



Conformal Therapy
Active Breathing Control (ABC)

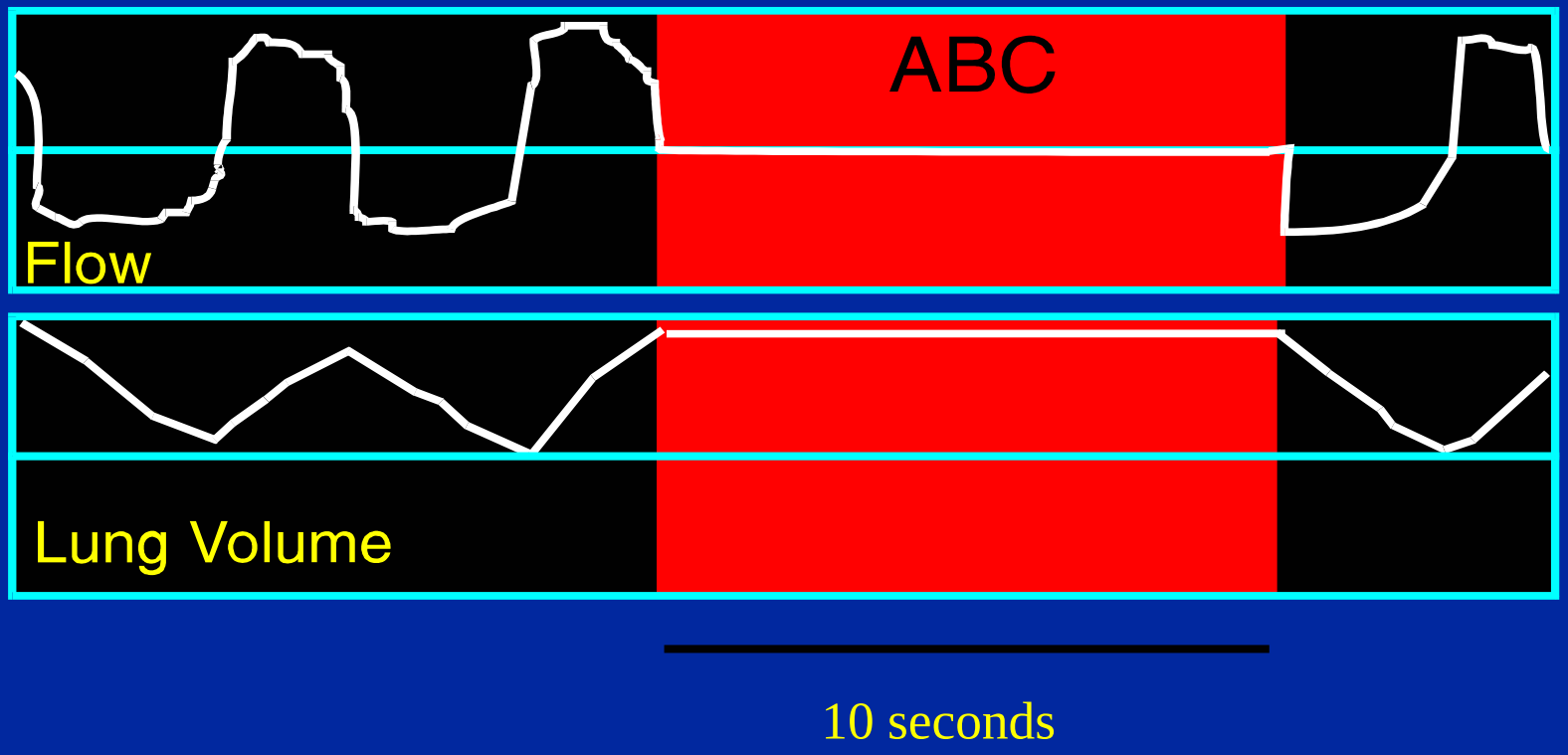




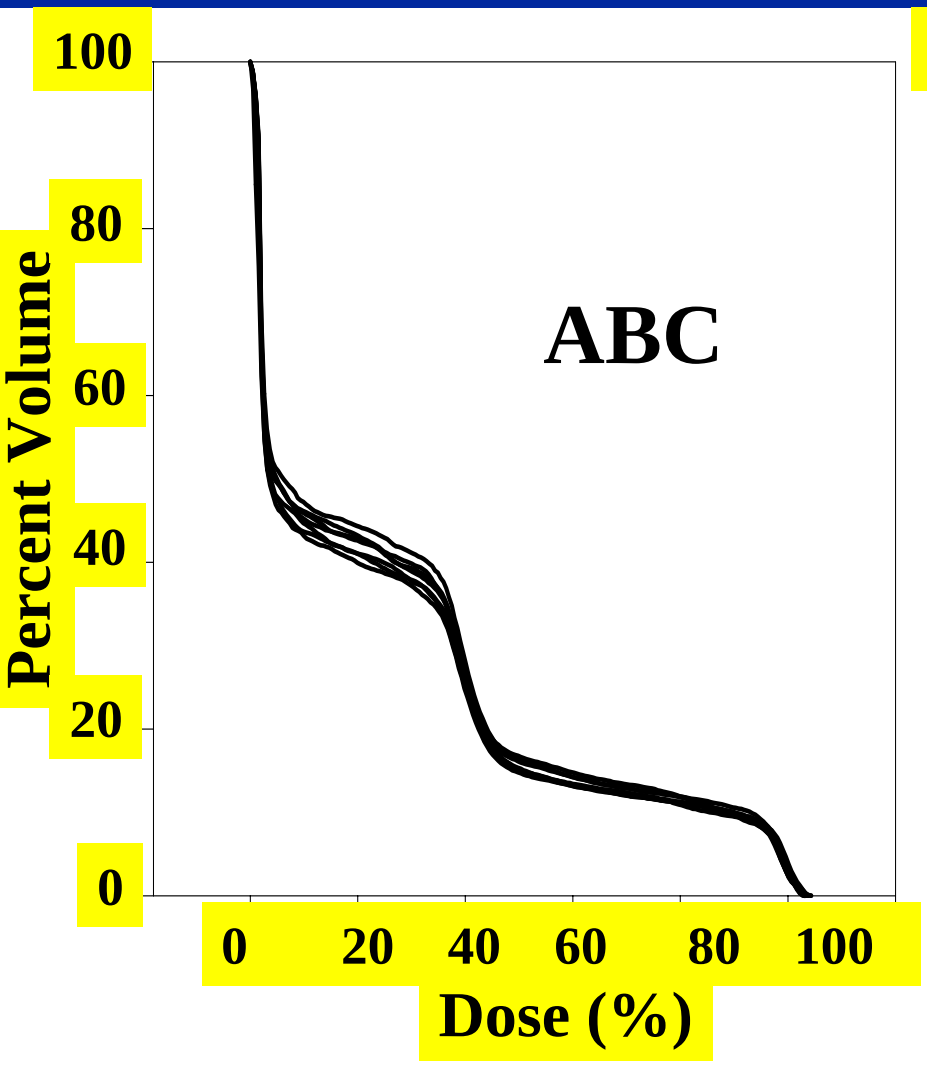
Conformal Therapy
Active Breathing Control (ABC)

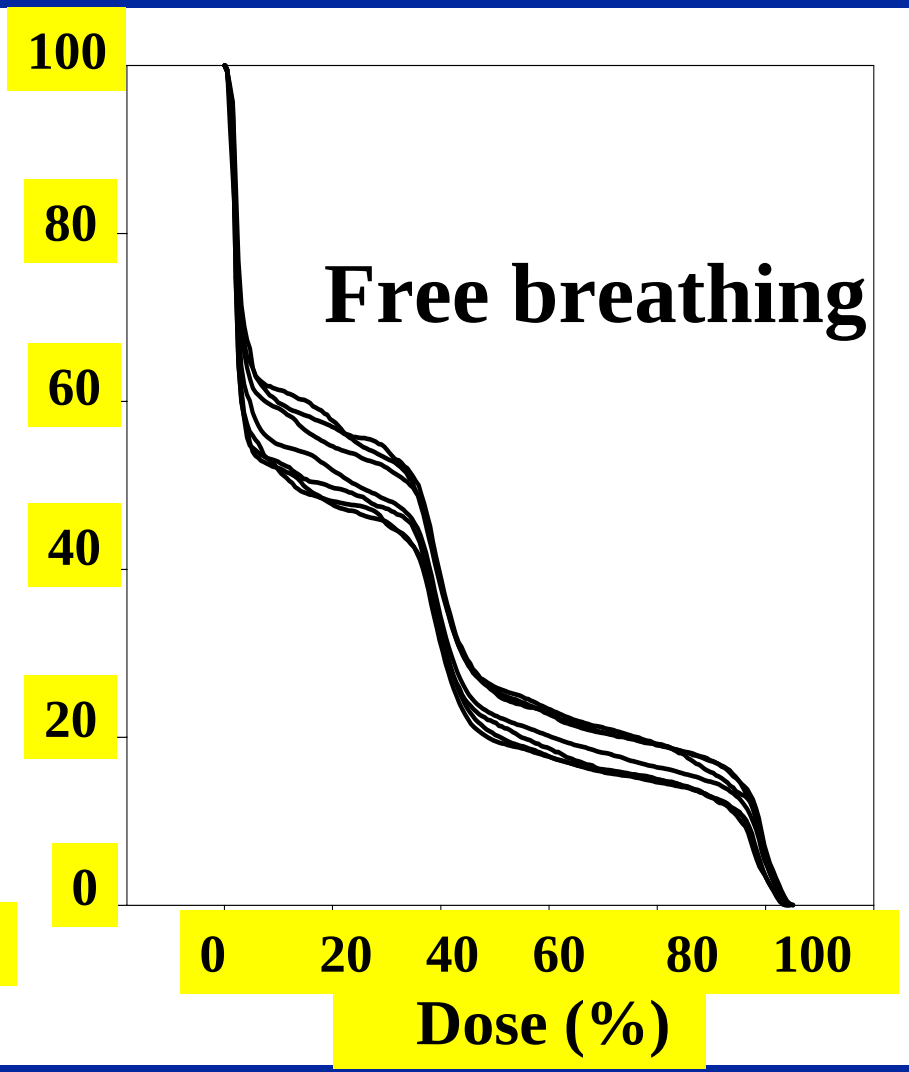
Courtesy of WBH

Active Breathing Control



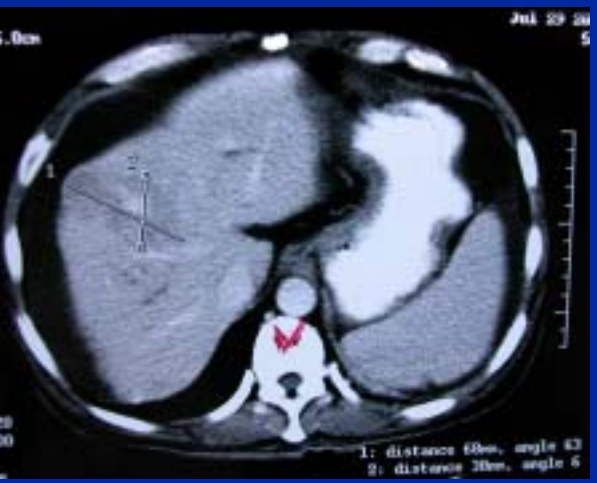
Mock Gall Bladder Treatment: Range of Liver DVHs



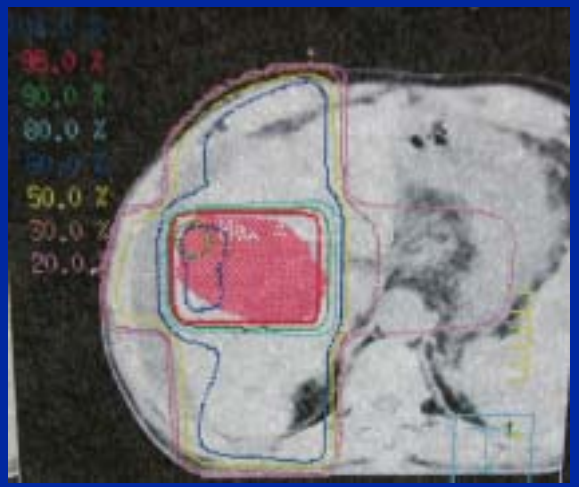


HCC in Some Situations managed by Radiation Therapy

- Severe liver cirrhosis with ascites
- After many times PEIT, tumor still progress
- Liver hilar LNs enlargement
- Tumors locate at S1 and S4
- Huge tumor
- Palliative treatment for bone or brain metastasis



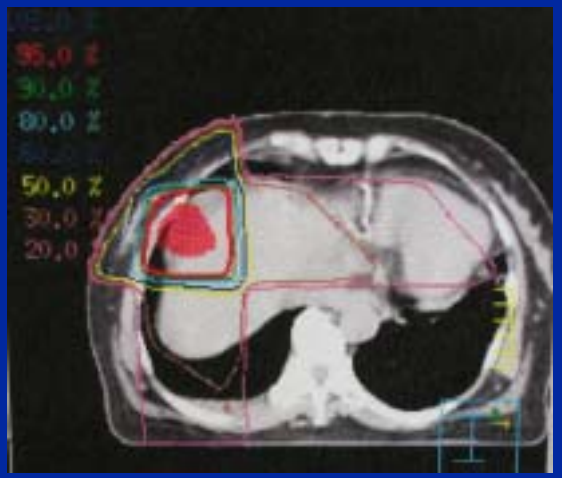
Before treatment



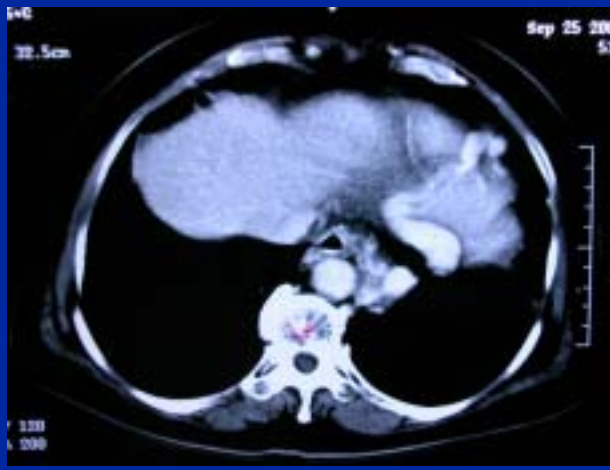
Treatment plan

3 months later

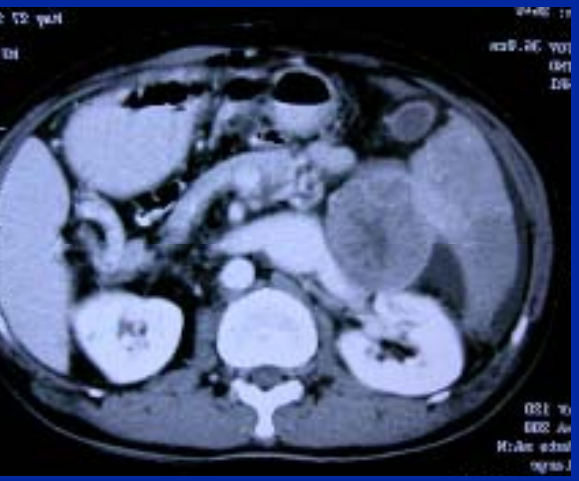
Before treatment



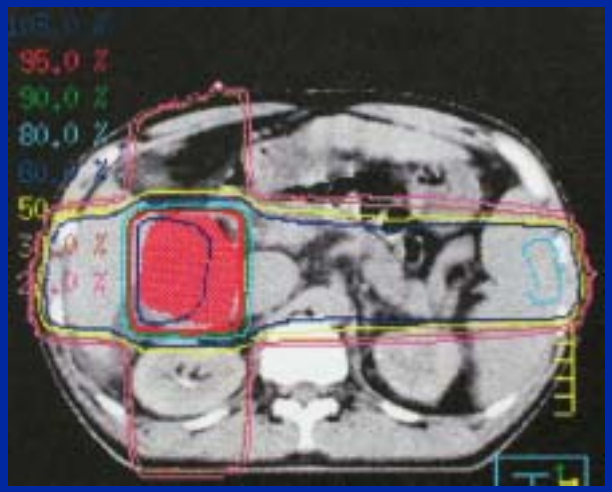
Treatment plan



2.5 months later

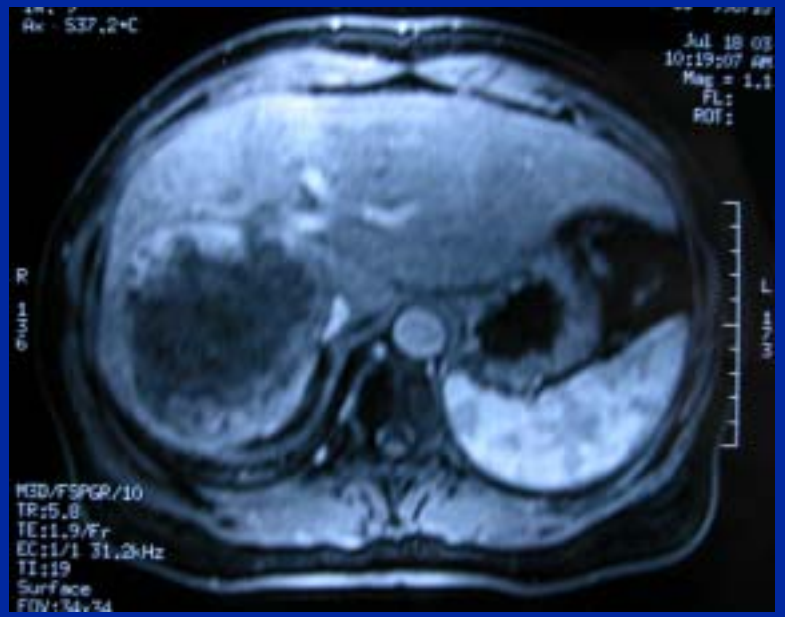


Before treatment



Treatment plan

2.5 months later



Huge HCC after RT

Post operation

The Effect of Concurrent Radiotherapy and Oral UFUR for Hepatoma

Chemopotentiation

- Modify the structure of DNA in such a way as to make it more sensitive to the action of radiation
- Inhibit the repair of sublethal damage produced by radiation
- Inhibit DNA synthesis

Antimetabolite agent

- 5-FU, a structure analogue of the DNA precursor thymine
- It works primarily as an irreversible inhibitor of the enzyme thymidylate synthelase

Cases Selection

- Performance Status: >70
- Age:<70
- WBC>4000
- GOT, GPT: limit within 3 times to normal value
- No jaundice
- Most of the tumor or PVT area can be treated within one radiation field, the dose-volume histogram show less than one half of the normal liver received 50% of prescribed dose

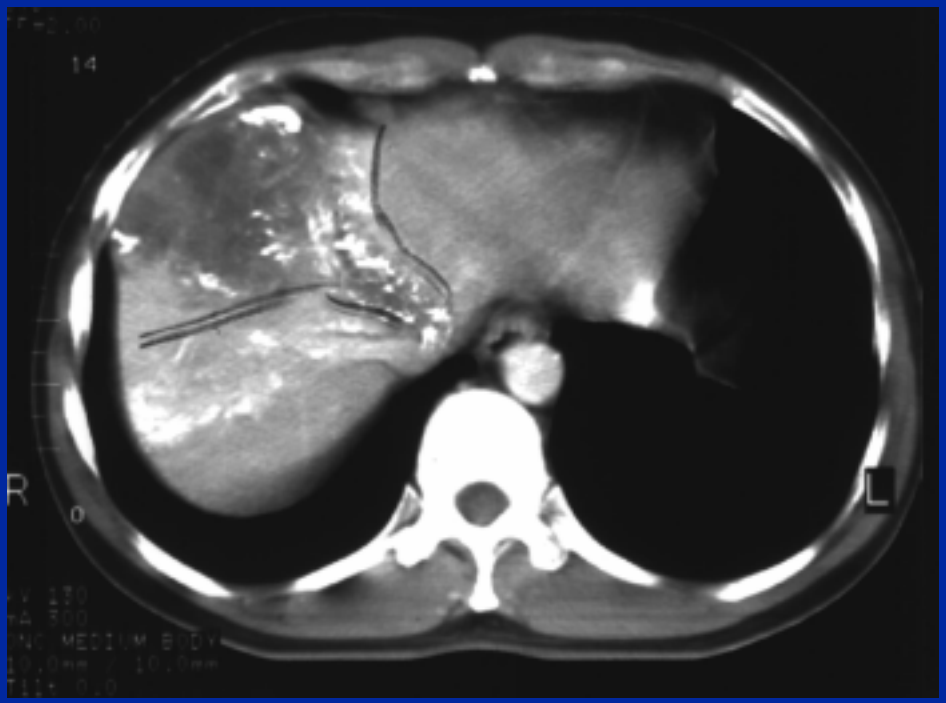
Radiation Dose

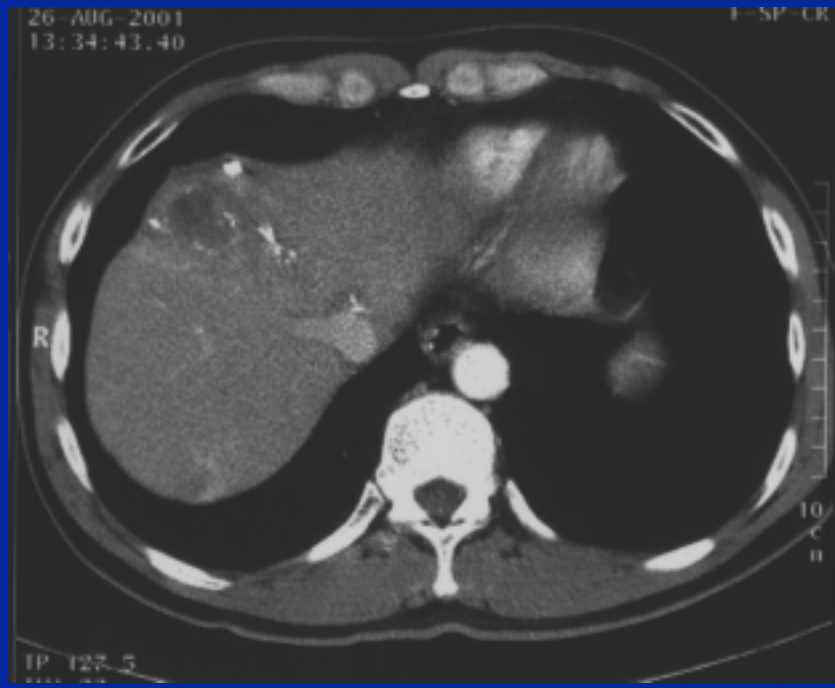
- 10 or 15 MV X-ray
- Dose: 250 cGy/ fr for 5500 cGy/ 22 fr or
  200 cGy/ fr for 6400 cGy/ 32 fr

ADAC Pinnacle treatment planning system—for 3-D conformal technique plan

UFUR

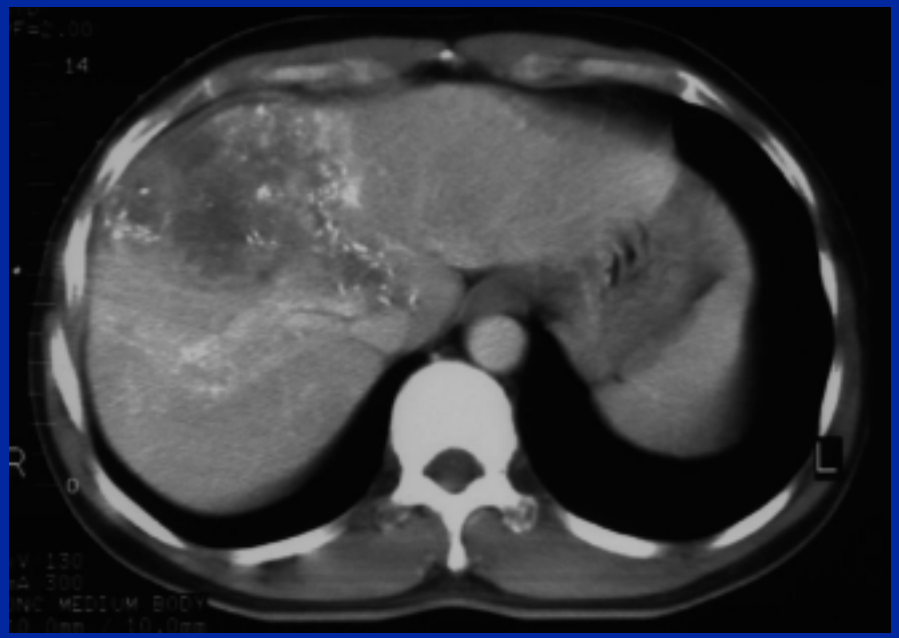
- Oral form---easy to carry on
- 2 tablets BID from day 1 to the end of R/T, at least CCRT for 4 weeks
- CBC and LFT before CCRT, at dose around 3000 cGy, and at the end of CCRT

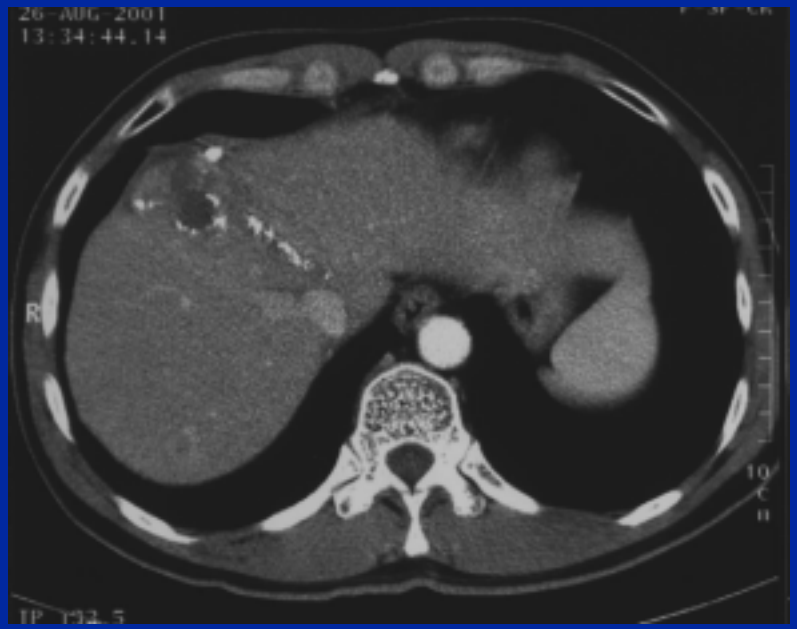




Before RT

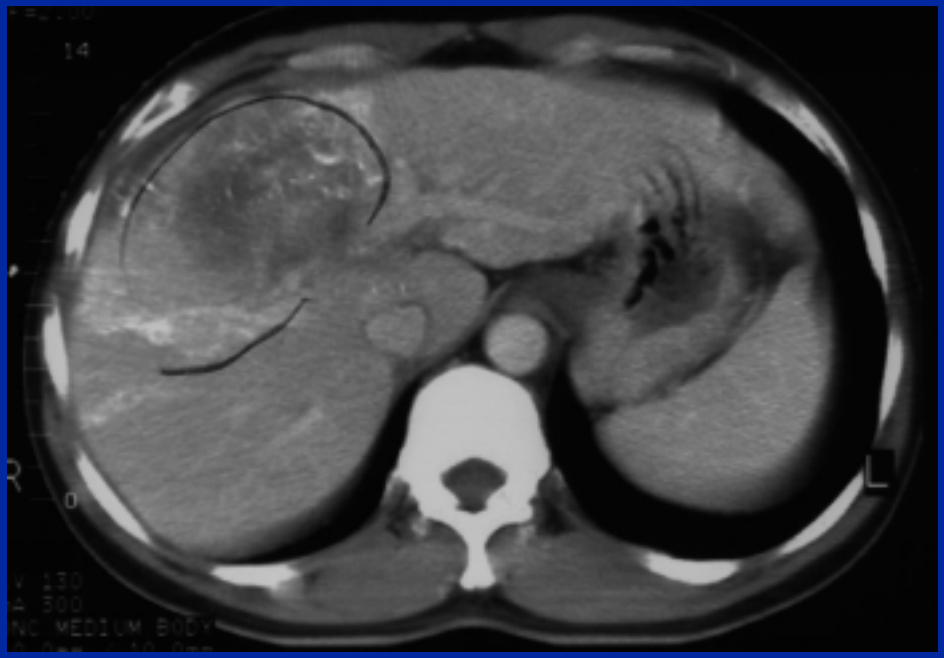
After RT

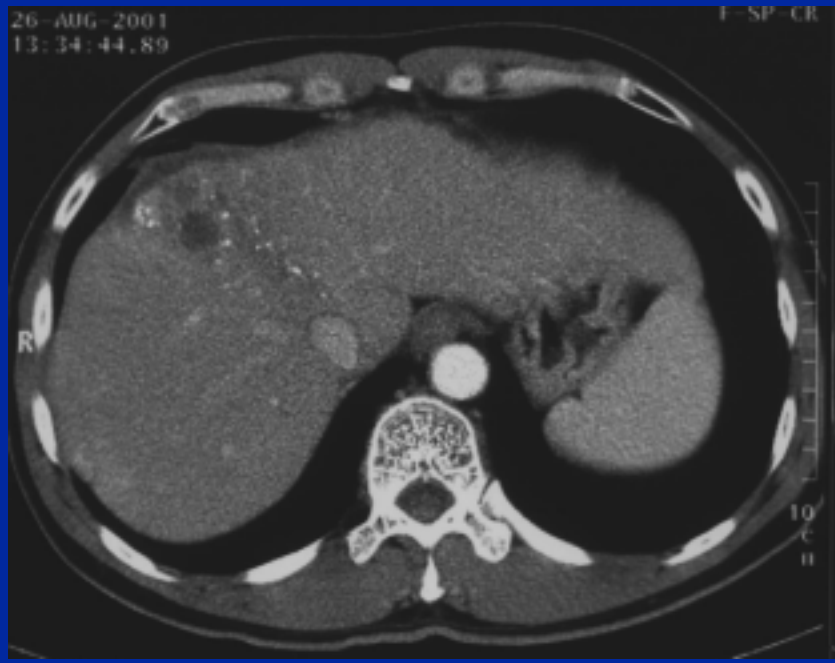




Before RT

After RT





Before RT

After RT

Conclusions

- Modern technology of radiotherapy can achieve precision targeted radiation dose to hepatoma and limit the damage of the adjacent normal tissues.
- Combined modalities treatment is the trend for hepatoma management in order to obtain better tumor control, good life quality and prolong survival for the patients.

中時晚報

光子刀療法

BID雙殺 肝癌細胞死光光

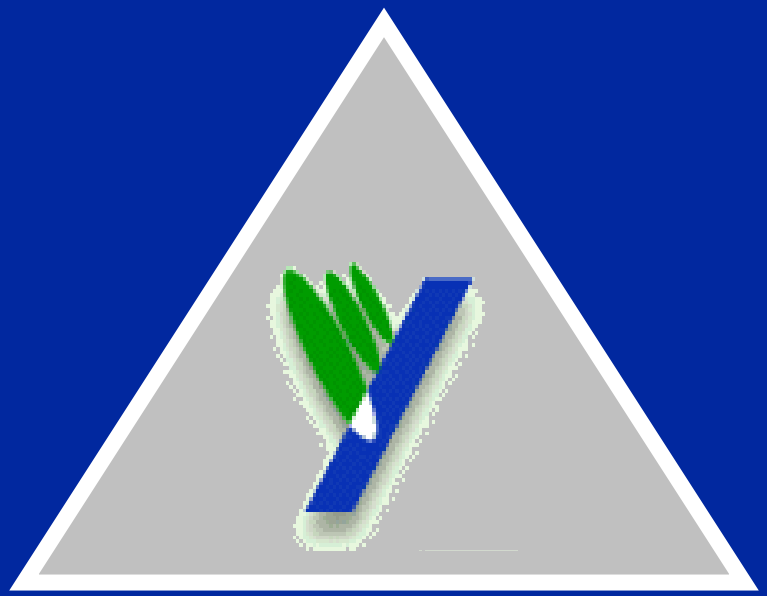
一天兩回爭取時間差 讓正常細胞回復生息 存活率提高3成 6成患者肝癌完全消失

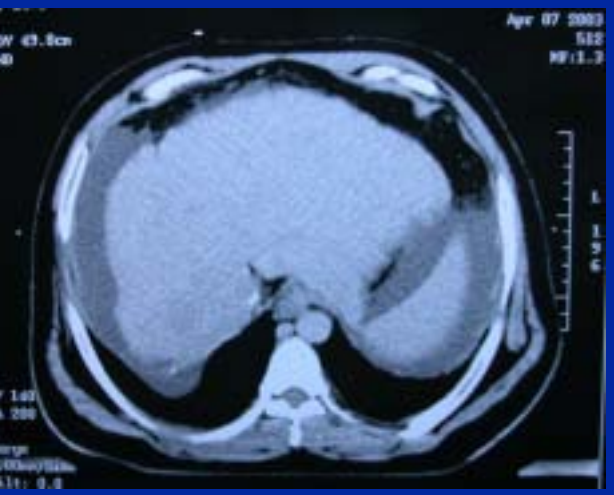
黃金足／台中報導

肝癌每四十天會長大一倍，最死肝癌要和時間賽跑！台中慈濟醫院和台大醫院合作，研發成功最新的「BID肝癌光子刀治療法」，採取時間差攻擊法，一天兩次光子刀殺死肝癌細胞，首批接受治療的患者，有高達八十二%的存活率，六成患者體內肝癌完全消失，創下國內罕見的肝癌存活率。

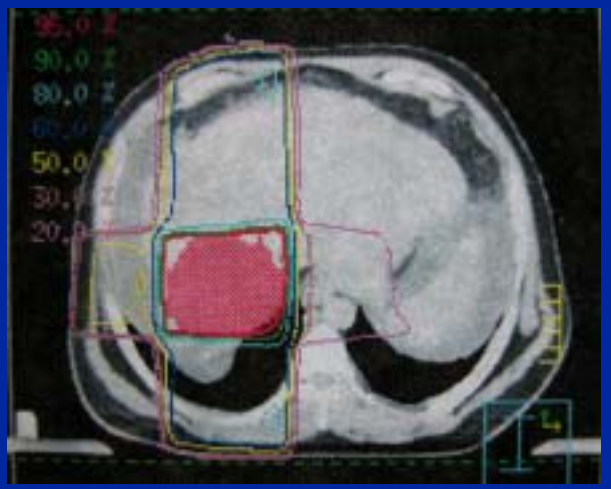
慈濟醫院光子刀治療中心主任王博民表示，新療法BID可以雙重打擊肝癌，是肝癌者最大的福音，尤其對於罕見小於五公分的肝癌，療效更佳。「BID光刀子」治療法的原理是利用肝癌細胞增生速度每快的特點，使用紅外線等向光刀子，每天上下午各給予一次治療，因為癌細胞DNA上午受到光刀子打擊後，隔六到八小時DNA又再次受到下午光刀子打擊，對癌細胞造成比單純光子刀治療更大的破壞力，也因為中間隔六到八小時之間的休息，正常肝臟細胞得以修補修補，再正常組織的傷害降到最低，慈濟醫院表示，經過一年半追蹤，第一批十九名接受BID光子刀療法的患者有八十二%的存活率，其中有近六成的患者體內癌細胞完全消失，整體來說，存活率較傳統光子刀治療提高三成以上，患者可就近到台大或慈濟醫院是否進行此種治療。

優質的醫療



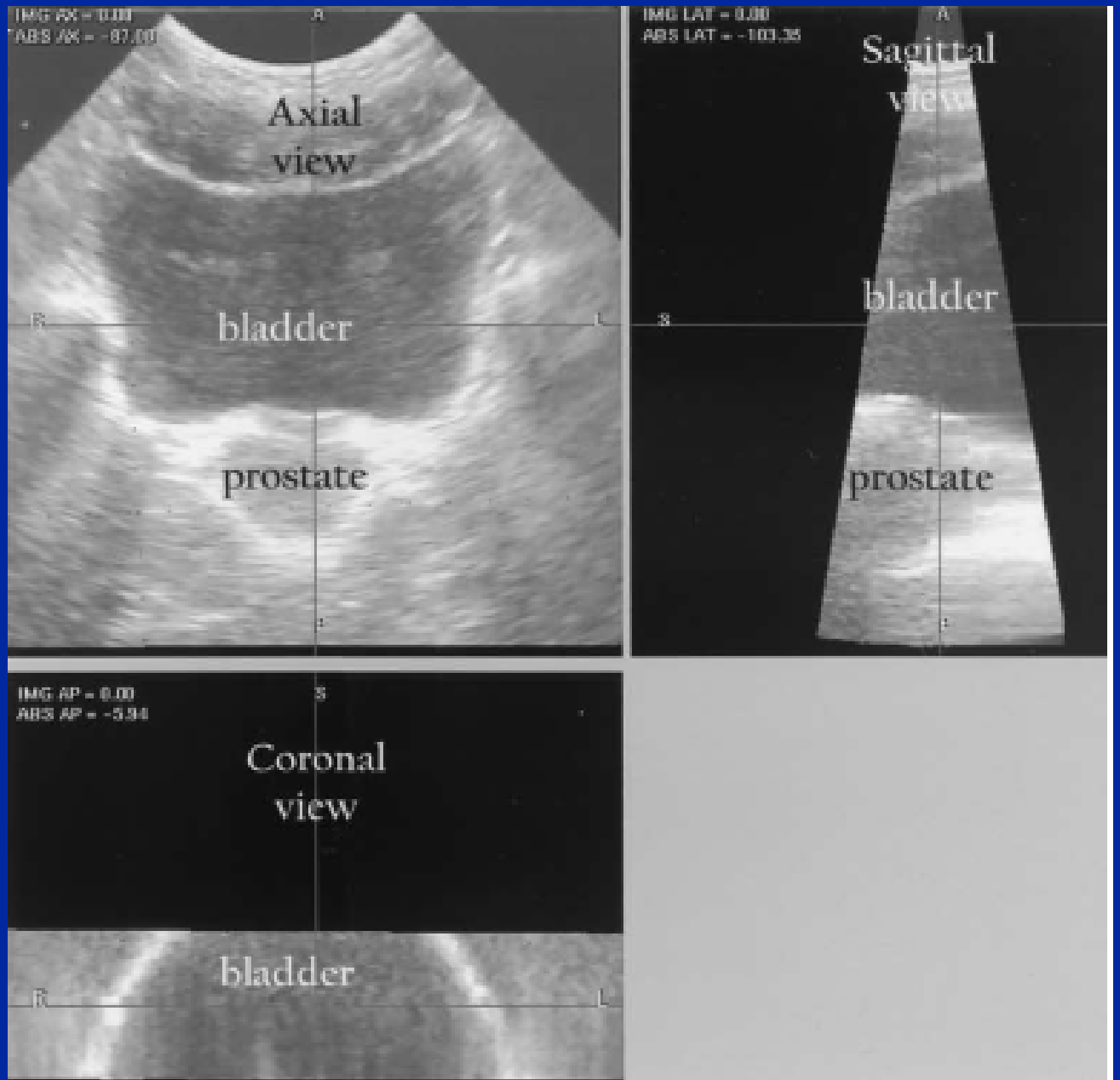


Before treatment



Treatment plan

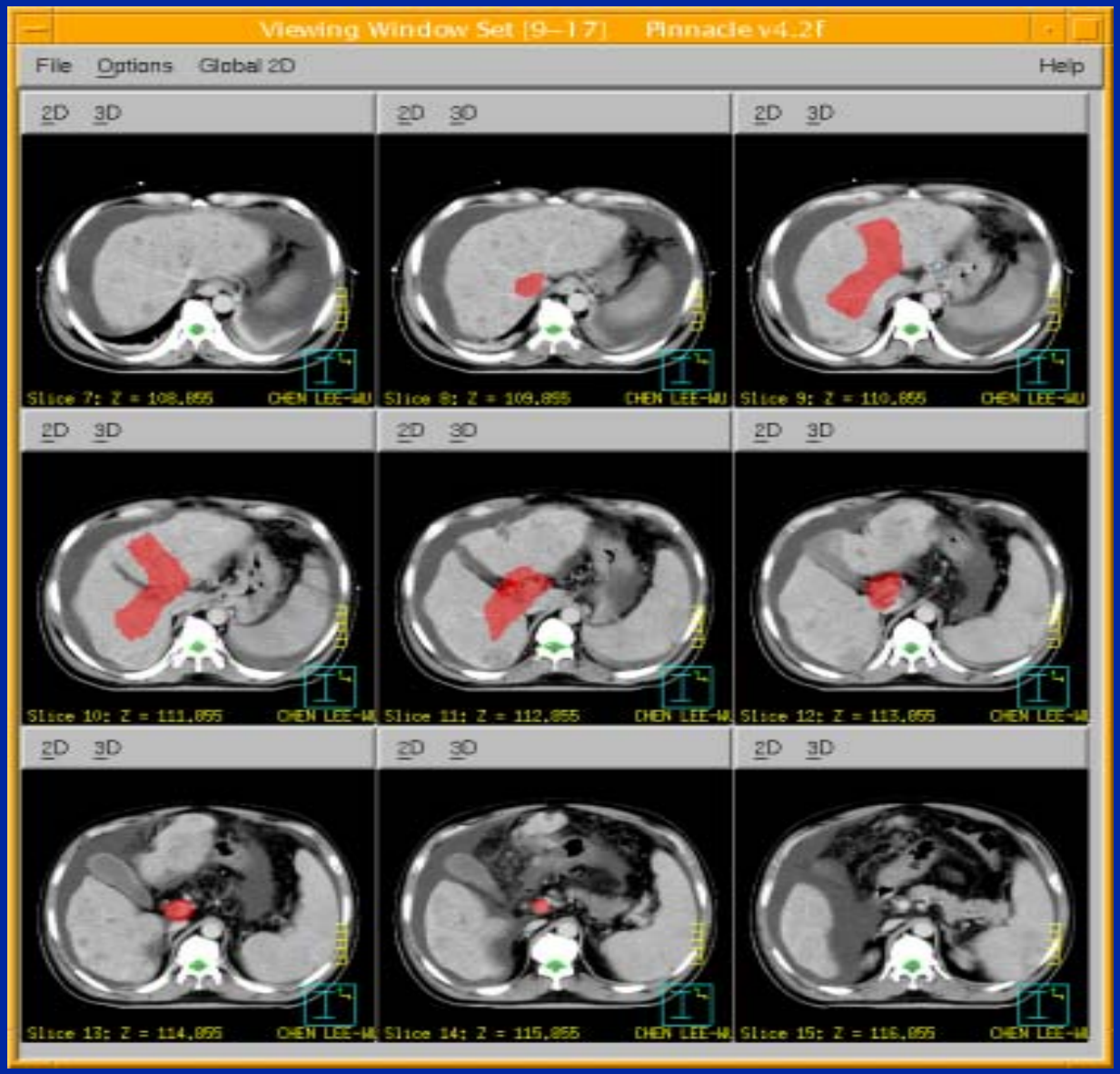
7 months later


Axial
view
bladder
prostate
Sagittal
view
bladder
prostate
Coronal
view
bladder

Patients' Data

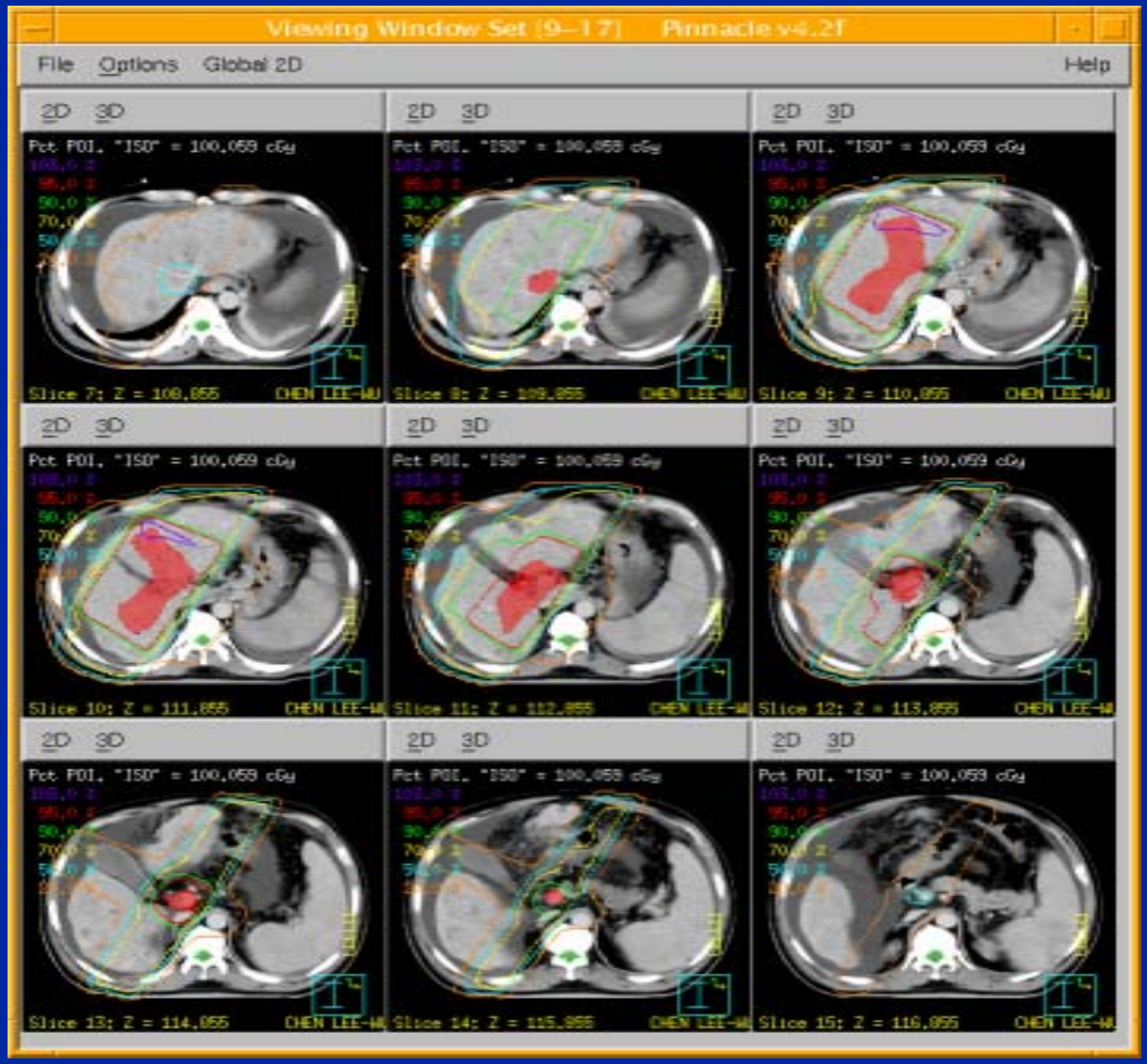
CHART	STATUS	R/TDATE	COMP	cGy	WK	NAU	VOM	WBC	LFT	IMAGES	F/U
288964	LPVT	2001/6/20	2001/8/20	6400	6	MILD	N	WNL	WNL	PROG	2001/10/2
102948	MPVT	2001/4/9	2001/6/7	6600	4	MILD	N	DEC	INC.	C.T.	2001/9/21
460099	RPVT	2001/4/13	2001/5/28	6600	6	MILD	OCC	WNL	INC.	LOSSF/U	2001/6/5
656141	IVC	2001/5/21	2001/0706	6400	5	MILD	N	WNL	WNL	PARTIAL	2001/10/3
657079	RPVT	2001/6/5	2001/7/20	6600	6	N	N	WNL	WNL	GOOD R.	2001/11/2
447600	LPVT	2001/8/13	2001/9/26	6600	6	MILD	N	WNL	WNL	PARTIAL	2001/11/9
117709	REC T.	2001/10/5	2001/11/21	6400	4	N	N	DEC	WNL	F/U	
655146	RPVT	2001/6/11	2001/7/26	6600	6	MILD	N	WNL	WNL	PARTIAL	2001/10/2
663055	MPVT	2001/8/31	2001/10/4	5750	4	N	N	DEC	WNL	PARTIAL	2001/11/1
907829	LPVT	2001/5/4	2001/6/19	6400	4	MILD	N	WNL	WNL	PROG	2001/10/1
260781	WPVT	2001/9/17	2001/11/2	6600	6	MILD	N	WNL	INC.	F/U	2001/11/1
672114	WPVT	2001/9/19	2001/11/3	6400	4	MILD	N	DEC	WNL	F/U	2001/11/2
435757	RPVT	2001/5/15	2001/6/28	6400	2	P	P	WNL	WNL	PARTIAL	2001/11/1

Target Definition



Beam Arrangement

Isodose Curve Distribution



Dose Volume Histogram