



# Dose-Volumetric Parameters Predicting Radiation-Induced Hepatic Toxicity in Unresectable Hepatocellular Carcinoma Patients Treated with Three Dimensional Conformal Radiotherapy

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## Background

- Transcatheter arterial chemoembolization (TACE) is one of the most popular forms of non-surgical treatment for unresectable hepatocellular carcinoma (HCC) patients.
- Sometimes, TACE is ineffective or unsuitable for several reasons:
  - dual blood supply around tumor capsule,
  - development of collateral blood vessels,
  - recanalized occluded vessel,
  - arterioportal or arteriovenous shunts,
  - massive portal vein thrombosis.
- Recent results of radiotherapy (RT) for unresectable HCC patients have been showed as promising, but radiation-induced hepatic toxicity (RIHT) is one of most important dose-limiting toxicities.
- The predicting the risk of RIHT following RT is important for HCC patients in clinical practice, but no consensus has been reached about which dose-volumetric parameters best predict the risk of RIHT.

## Aims

- To identify dose-volumetric parameters associated with the risk of RIHT in HCC patients treated with three-dimensional conformal radiotherapy (3D-CRT).

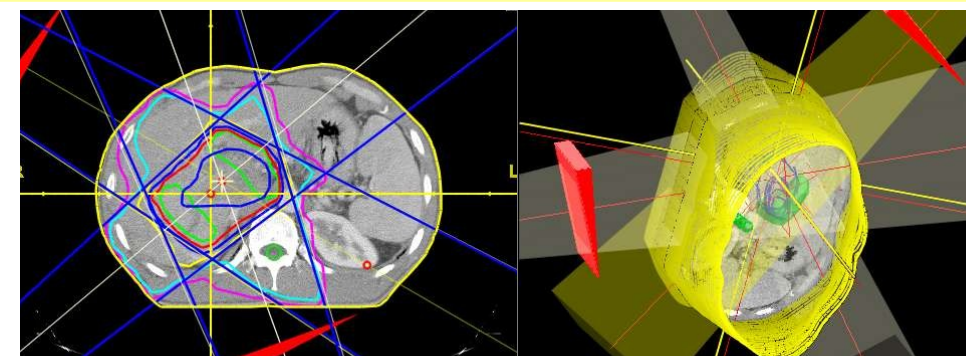
## Methods

### Patients

- Between July 2001 and January 2006, 124 unresectable HCC patients underwent 3D-CRT in National Cancer Center.
- 105 patients of them were retrospectively evaluated
- Inclusion criteria :
  - Child-Pugh class A or B,
  - Eastern Cooperative Oncology Group score  $\leq 2$ ,
  - without distant metastasis,
  - radiation dose of  $\geq 44$  Gy

### Radiation therapy

- 3D-CRT was delivered using linear accelerator with 6 or 15 MV X-rays.
- Total dose of 44-54 Gy (median, 54 Gy), in daily fraction of 2-3 Gy.



### Radiation-induced hepatic toxicity evaluation

- RIHT was scored using the Common Terminology Criteria for Adverse Events software version 3.0 in the absence of progressive disease.

Grade	Level of transaminases and alkaline phosphatase
0	Within the pre-treatment level or upper limit of normal (ULN)
1	> ULN - 2.5×ULN
2	> 2.5×ULN - 5.0×ULN
3	> 5.0×ULN - 20.0×ULN
4	> 20.0×ULN
5	Death

## Statistical analysis

- Univariate and multivariate logistic regression analysis (SAS v8.02)

## Result

### Patient characteristics

Characteristics	Distribution, n (%)	Characteristics	Distribution, n (%)
Gender	Male 92 (87.6)	Child-Pugh classification	A 85 (81.0)
	Female 13 (12.4)		B 20 (19.0)
Age (year)	Median (range) 55 (26-78)	AJCC tumor stage	T2 27 (25.7)
	$\leq 60$ 70 (66.7)		T3 72 (68.6)
$> 60$ 35 (33.3)	T4 6 (5.7)		
HBV	No 18 (11.2)	CLIP score	1 20 (19.1)
	Yes 87 (82.8)		2 42 (40.0)
PVT	No 45 (42.9)		3 29 (27.6)
	Yes 60 (57.1)		4 14 (13.3)
AFP (IU/mL)	< 400 49 (46.7)	Previous treatment	No 14 (13.3)
	$\geq 400$ 56 (53.3)		Yes 91 (86.7)

HBV = Hepatitis B virus; AFP =  $\alpha$ -fetoprotein; PVT = portal vein thrombosis; AJCC = American Joint Committee on Cancer; CLIP = the cancer of the liver Italian Program.

### Observation rate of RIHT

Grade	No. of patients (%)
0	71 (0.0)
1	21 (20.0)
2	7 (6.7)
3	5 (4.8)
4	1 (1.0)
5	0 (0.0)

- Median time for development of RIHT was 1 month after RT (range, 1 week - 3 months).
- Median recover time of RIHT after development was 2 months after RT (range, 1 - 4 months).

### Analysis of Clinical parameters on risk of RIHT

Parameters	Observed rate* of $\geq$ grade 2 RIHT (%)	P-values	
		Univariate	Multivariate
Gender (Male vs. Female)	13/92 (14.1) vs. 0/13 (0.0)	0.970	NS <sup>†</sup>
Age (years, $\leq 60$ vs. $> 60$ )	11/70 (15.7) vs. 2/35 (5.7)	0.160	NS <sup>†</sup>
HBV (No vs. Yes)	1/17 (5.9) vs. 12/88 (13.6)	0.389	NS <sup>†</sup>
PVT (No vs. Yes)	2/45 (4.4) vs. 11/60 (18.3)	0.048	NS <sup>†</sup>
AFP (IU/MI, < 400 vs. $\geq 400$ )	5/49 (10.2) vs. 8/56 (14.3)	0.528	NS <sup>†</sup>
Child Class (A vs. B)	9/85 (10.6) vs. 4/20 (20.0)	0.258	NS <sup>†</sup>
Tumor stage (T2 vs. T3-4)	2/27 (7.4) vs. 11/78 (14.1)	0.371	NS <sup>†</sup>
CLIP score (< 3 vs. $\geq 3$ )	4/62 (6.5) vs. 9/43 (20.9)	0.035	NS <sup>†</sup>
Previous Tx (No vs. Yes)	2/14 (14.3) vs. 11/91 (12.1)	0.816	NS <sup>†</sup>

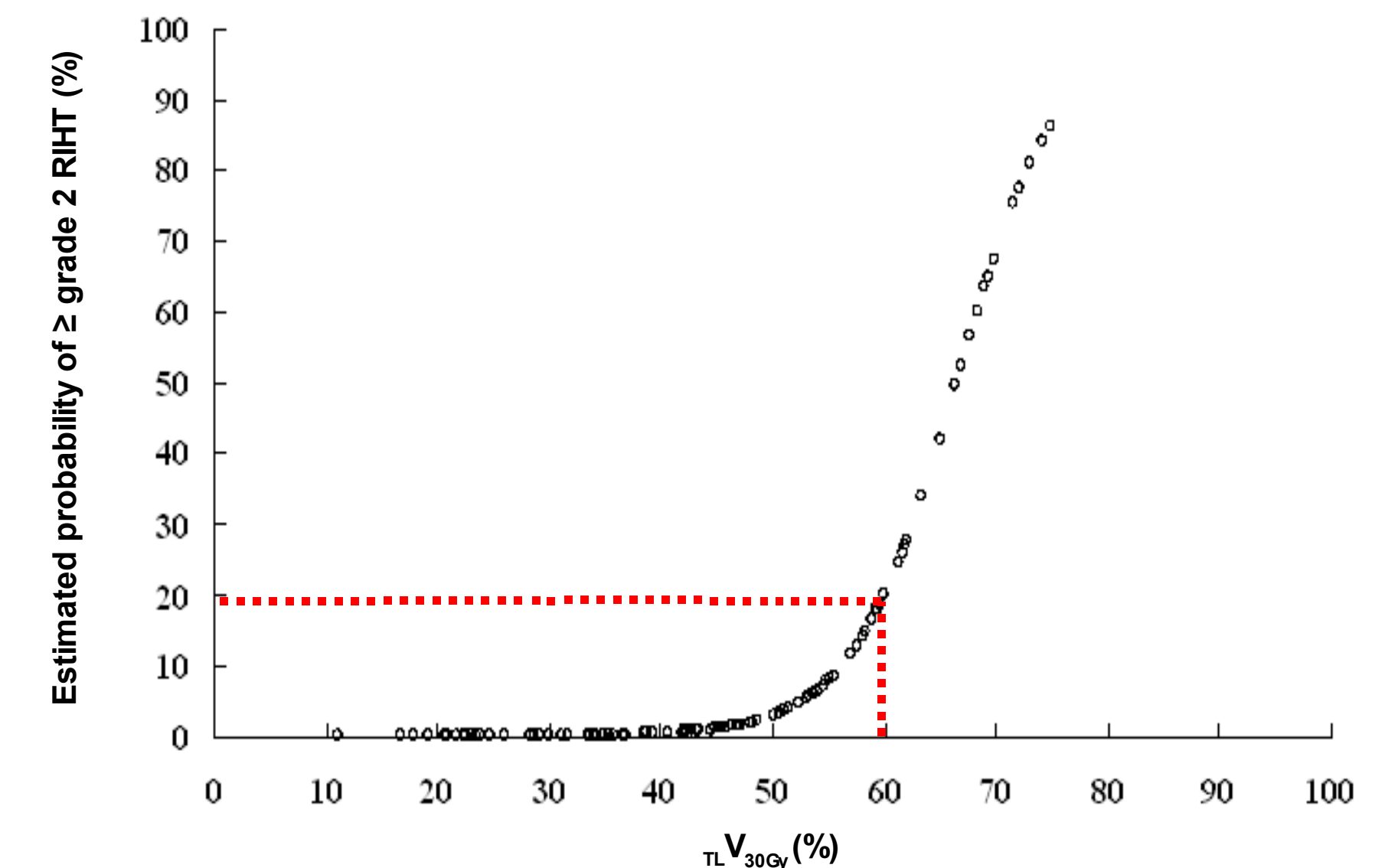
\*Observed rate = No. of patients with  $\geq$  grade 2 RIHT / No. of patients at risk (%); NS<sup>†</sup> = not significant.

## Analysis of Dose-volumetric parameters on risk of RIHT

Parameters	RIHT ( $\mu \pm \sigma$ )		P-values	
	< grade 2	$\geq$ grade 2	Univariate	Multivariate
GTV (cm <sup>3</sup> )	388.2 $\pm$ 463.8	388.2 $\pm$ 463.8	0.223	NS <sup>†</sup>
NLV (cm <sup>3</sup> )	560.7 $\pm$ 353.9	560.7 $\pm$ 353.9	0.075	NS <sup>†</sup>
TLV (cm <sup>3</sup> )	1266.7 $\pm$ 323.6	1266.7 $\pm$ 323.6	0.107	NS <sup>†</sup>
Radiation dose <sup>†</sup> (Gy)	53.3 $\pm$ 2.3	53.3 $\pm$ 2.3	0.526	NS <sup>†</sup>
D <sub>mean</sub> (Gy)	53.7 $\pm$ 1.1	53.7 $\pm$ 1.1	<0.001	NS <sup>†</sup>
$_{TL}V_{20Gy}$ (%)	50.3 $\pm$ 14.0	50.3 $\pm$ 14.0	<0.001	NS <sup>†</sup>
$_{TL}V_{25Gy}$ (%)	72.8 $\pm$ 5.7	72.8 $\pm$ 5.7	<0.001	NS <sup>†</sup>
$_{TL}V_{30Gy}$ (%)	46.8 $\pm$ 13.7	46.8 $\pm$ 13.7	<0.001	<0.001
$_{TL}V_{35Gy}$ (%)	69.4 $\pm$ 5.4	69.4 $\pm$ 5.4	<0.001	NS <sup>†</sup>
$_{TL}V_{40Gy}$ (%)	43.5 $\pm$ 13.7	43.5 $\pm$ 13.7	<0.001	NS <sup>†</sup>
NTCP (%)	66.4 $\pm$ 5.5	66.4 $\pm$ 5.5	<0.001	NS <sup>†</sup>

GTV = gross tumor volume; NLV = normal liver volume; TLV = total liver volume; D<sub>mean</sub> = Mean dose to the normal liver;  $_{TL}V_{20Gy}$ ,  $_{TL}V_{25Gy}$ ,  $_{TL}V_{30Gy}$ ,  $_{TL}V_{35Gy}$ , and  $_{TL}V_{40Gy}$  = the percentage of the total liver volume receiving  $\geq 20$  Gy,  $\geq 25$  Gy,  $\geq 30$  Gy,  $\geq 35$  Gy, and  $\geq 40$  Gy; NTCP = normal tissue complication probability;  $\mu$  = mean;  $\sigma$  = standard deviation; radiation dose<sup>†</sup> = equivalent dose in 2 Gy fractions ( $\alpha/\beta$  ratio = 10).

### Risk of $\geq$ grade 2 RIHT according to $_{TL}V_{30Gy}$



$_{TL}V_{30Gy}$	Observed rate of $\geq$ grade 2 RIHT (%)	P-value
$\leq 60\%$	2 / 85 (2.4)	<0.001
$> 60\%$	11 / 20 (55.0)	

## Conclusion

- $_{TL}V_{30Gy}$  is particularly useful for predicting the risk of  $\geq$  grade 2 RIHT.
- $_{TL}V_{30Gy}$  should be limited to less than 60%, whenever possible, to minimize the risk of  $\geq$  grade 2 RIHT following 3D-CRT for unresectable HCC patients.