

Individualized dosimetry treatment planning for liver irradiation

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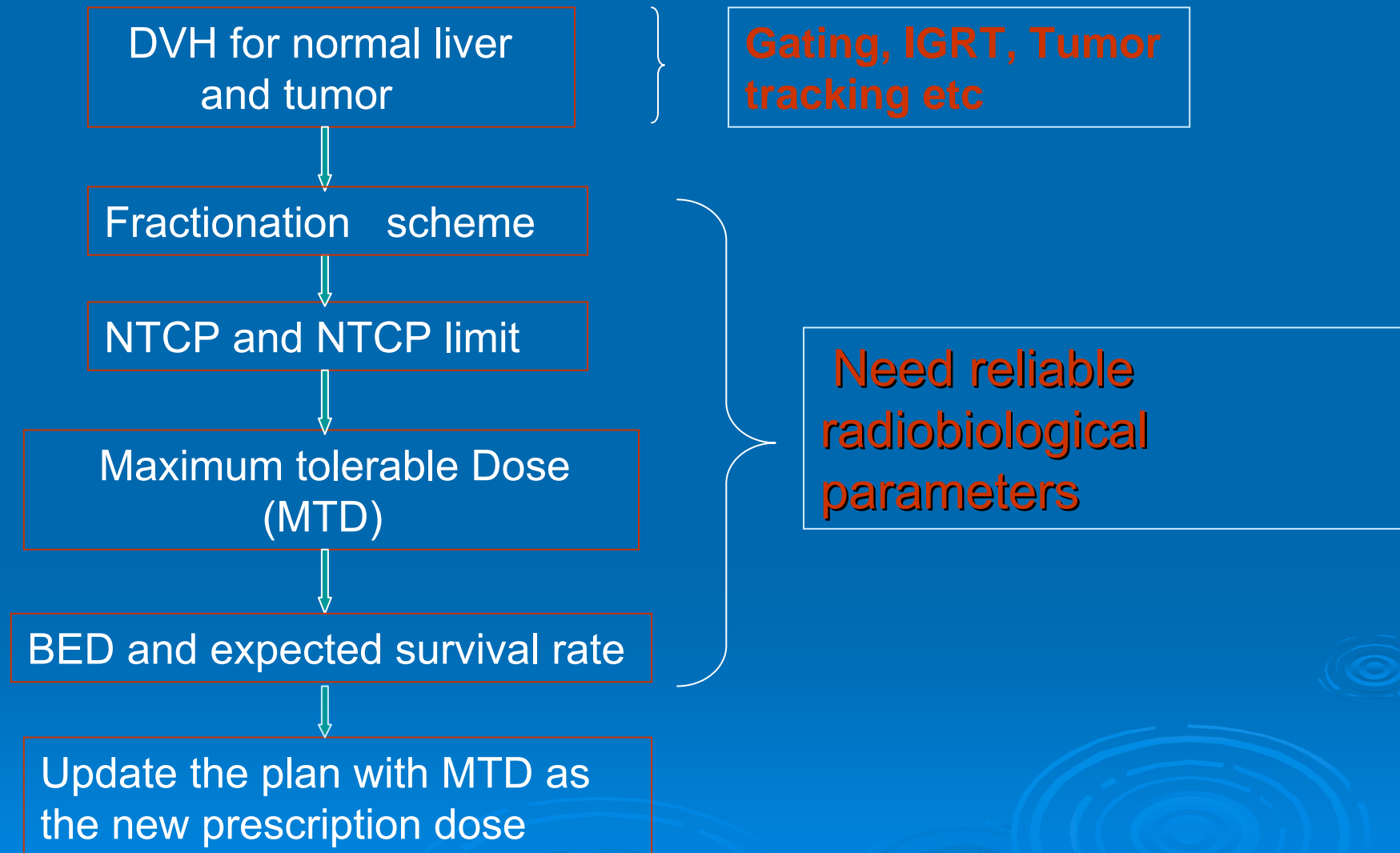
Outline

- Introduction
- Materials
- Methods
- Results
- Conclusions

Introduction

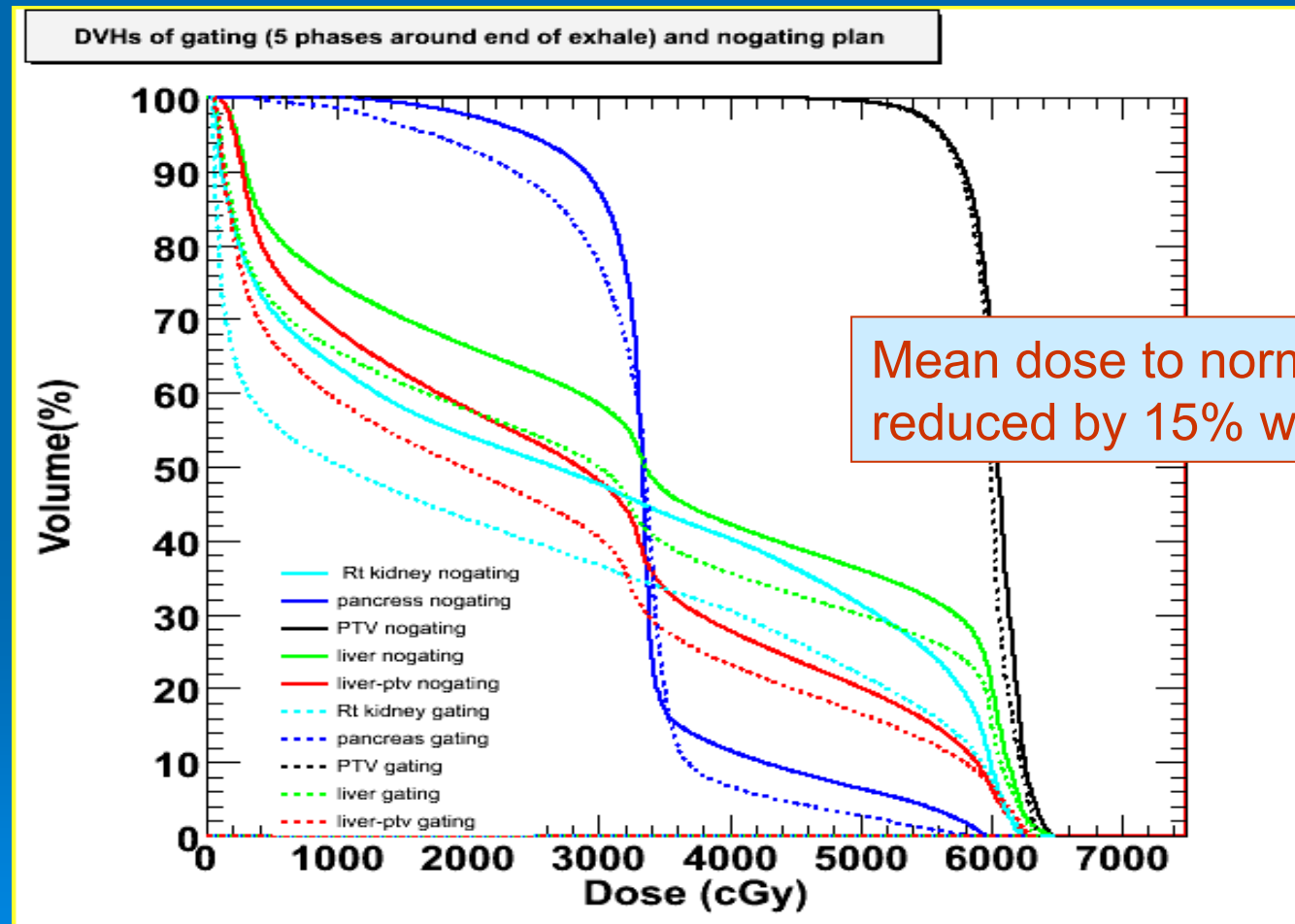
- Availability of IG-IMRT/gating for liver targets invites alternative or more effective RT strategies.
- Various prescribed doses and dose rates are being used clinically (eg 61.5 Gy 1.5Gy/fx, 53.6 Gy 4.88Gy/fx) for RT liver tumor treatment.
- New hypofractionation regimens (RTOG 0438) were initiated: 10 fractions @3.5Gy/fx, 4.0Gy/fx, 4.5Gy/fx and 5.0Gy/fx.
- Allow to evaluate fractionation schemes and design individualized treatment plans

Flow of an individualized treatment plan



Gating vs non-gating plan

normal tissue sparing and tumor dose escalation



Dose fractionation scheme vs outcomes

Authors	Patient no.	Median prescribed dose	Fraction scheme (Gy/fx)	Treatment time (day)	Median survival rate (month)	Reference
S. X. Liang etc	128	53.6	4.88	28	20	Cancer Vol103, 218 (2005)
L.Dawson etc.	81	61.5	1.5	39	11	J. Clin Onco Vol18, 2210 (2000), Sem. Rad. Oncol 273 (2005)
J. Seong etc	83	55	1.8	43	6	Int. J. Rad. Onco Biol. Phys. 55 329 (2003)
J. Seong etc.	51	45	1.8	35	9	
J. Seong etc.	24	32.5	1.8	25	13	

Survival rate and tumor cell proliferation

- (1) Death probability of a liver cancer patient with K tumor cell in the tumor is given by

$$p = \begin{cases} 1 & K > K_{cr} \\ 0 & K < K_{cr} \end{cases}$$

- (2) Assume that the distribution of K_{cr} among patient population follows a Gaussian distribution.

$$S(D, \tau) = 1 - \frac{1}{\sqrt{2\pi}\sigma_{k_{cr}}} \int_{-\infty}^K e^{-\frac{(K_{cr}-K_{50})^2}{2\sigma_{k_{cr}}^2}} dK_{cr}$$

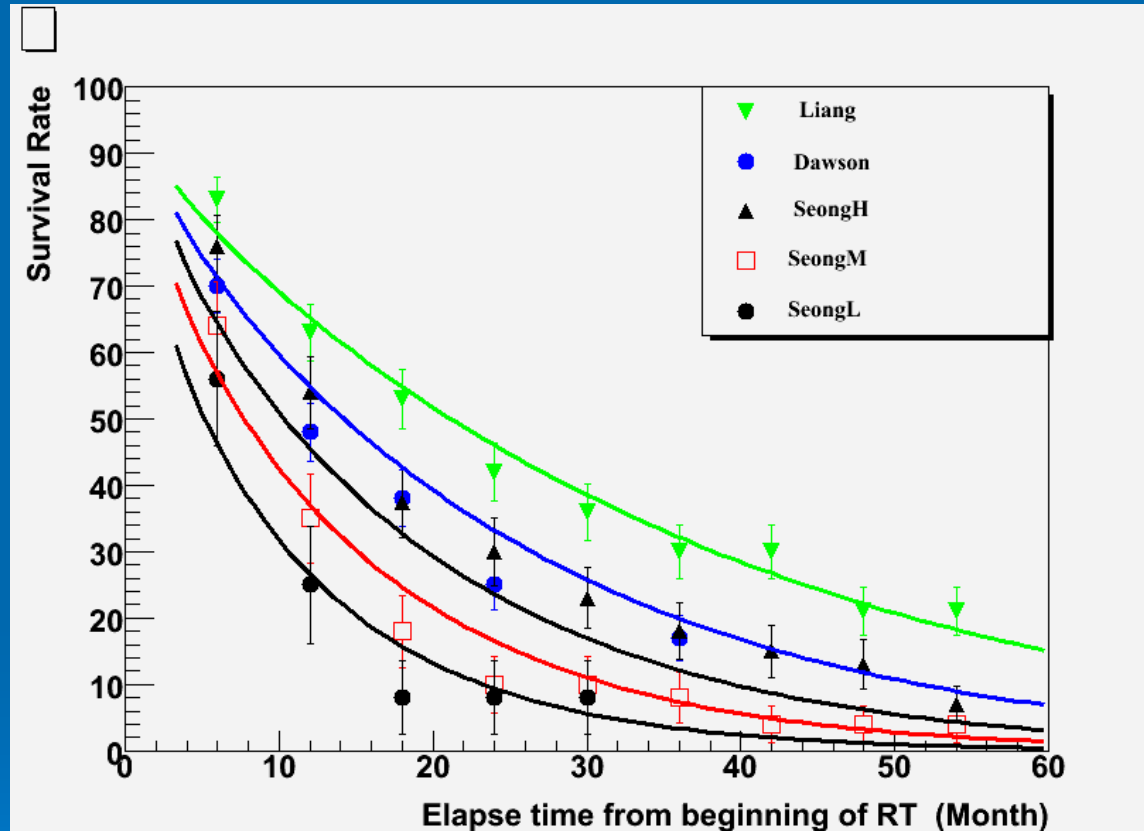
- (3) We used the following equation to describe time dependence τ of tumor cells from beginning of radiation treatment to time

$$K = K_0 e^{-\left[\alpha \left(1 + \frac{d}{\alpha/\beta}\right) D - \gamma T - (\gamma(\tau - T))^\delta \right]}$$

where $\gamma = \ln 2 / T_b$.

Gompertzian tumor growth model

Fitting results



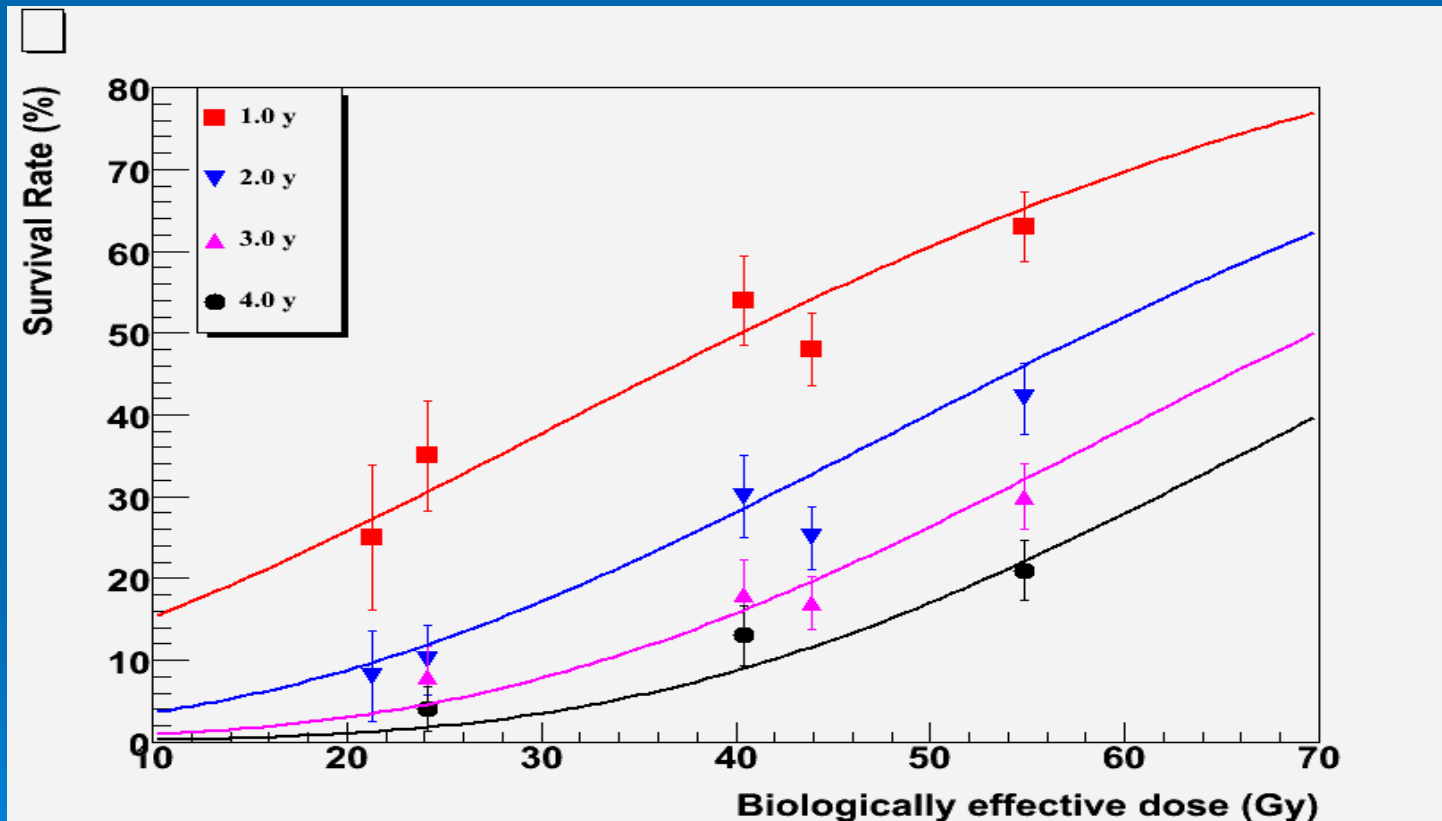
$K_0=1244\pm 16$
 $\alpha=0.010\pm 0.002 \text{ (Gy}^{-1}\text{)}$
 $\alpha/\beta=14\pm 2.0 \text{ (Gy)}$
 $T_b=110\pm 7 \text{ days}$
 $K_{50}=2625\pm 55$
 $\sigma=924\pm 71$
 $\delta=0.20\pm 0.01$

$$error = p_i \sqrt{\frac{1 - p_i}{N_i}}$$

Euro. J. of Surg. Oncol
 25 321-329 (1999)

Survival rate at different time

$$BED = (1 + d/\alpha\beta) * D - \gamma T / \alpha$$



Lyman model and fractionation scheme

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-x^2/2} dx$$

$$t = (D - TD_{50}(v)) / m \cdot TD_{50}(v)$$

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n}$$

$$v = V_{eff} = \sum_i v_i (D_i / D_{max})^{1/n}$$

$$D_i(d_{ref}) = \frac{(\alpha / \beta + d)}{(\alpha / \beta + d_{ref})} D_i(d)$$

For normal liver $\alpha/\beta=2$ Gy

Two sets of Lyman model parameters were used for the calculations of NTCP

parameter set 1: (1.5 Gy/fx
Dawson LA etc)

**TD50=40.5 Gy, m=0.28 and
n=1.1**

Parameter set 2: (4.6 Gy/fx
Liang SX etc)

**TD50=39.8 Gy, m=0.12 and
n=0.97**

Dose escalation based on NTCP

Lyman model parameters: $n=0.97$, $m=0.12$, $TD50(1)=39.8$ Gy

RT regimen for 3 liver patients	Mean dose (Gy) and calculated NTCP	BED (Gy) and expected 1 year survival rate	Escalated prescription dose (Gy) for NTCP<10%	BED (Gy) and expected 1 year survival rate
2.05 GyX22 5fx/week	20.3, 0.04%	32, 44%	64	45.5, 55%
1.8Gyx30 5fx/week	22.0, 0.05%	34, 40%	75	48, 58%
1.8Gyx25 5fx/week	22.3, 0.06%	29, 37%	62	40, 50%

NTCP are calculated using parameters of Set 1 with exception of 2 and 3 Gy per fraction of which NTCP are calculated using parameters of Set 2. The dose/fx, marked by *, are those recommended in RTOG 0438. Other regimens produce nearly the same BED for tumor as that for the proven dose fractionation regimen (1.5 Gy/fx and 10 fractions/wk).

dose /fx (Gy)	fraction /wk	Total fraction	Pres. Dose (Gy)	Treatment time (day)	BED for tumor (Gy)	Veff(%)=30-35 NTCP (%)	Veff(%)=35-40 NTCP(%)	MTD(10% NTCP at Veff=40%) (Gy)	SR(1y) (%) at MTD
2	5	33	66	45	47.1	0-0.4	0.4-3.3	71.8	61
3	3	21	63	47	46.9	0.7-6.5	6.5-28	57.4	52
3.5*	5	10	35	12	36.2	0.2-0.3	0.3-0.4	84.9	85
4	3	13	52	29	48.6	0.7-1.2	1.2-2.1	77.9	78
4*	5	10	40	12	43.9	0.3-0.5	0.5-0.8	77.9	84
4.5*	5	10	45	12	51.9	0.6-1.0	1.0-1.6	71.7	82
5*	5	10	50	12	60.3	1.0-1.8	1.8-3.2	66.7	81
5	2	10	50	33	47.1	1.0-1.8	1.8-3.2	66.7	71
5.5	2	8	44	26	44.9	0.8-1.5	1.5-2.5	62.2	72
9.0	1	4	36	21	45.9	1.5-2.9	2.9-5.2	42.4	60
19	1	1	19	1	44.2	1.6-3.0	3.0-5.3	22	58

Conclusions

- A plausible set of radiobiological parameters has been obtained based on clinical RT data for primary liver tumor: $\alpha=0.01$ (Gy^{-1}), $\alpha/\beta=14$ (Gy) and $T_b=110$ day.
- These parameters may be used to evaluate different fractionation schemes and to design new individualized treatment strategies for liver tumor.
- Regimens with dose per fraction between 3.5 to 5 Gy may lead to improved one-year survival rates (around 80%)