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RADIATION TOLERANCE OF THE LIVER IN RELATION TO THE PRESERVED FUNCTIONAL CAPACITY

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The radiation tolerance of the liver was investigated in 12 patients, 11 of them with liver cirrhosis, treated for hepatocellular carcinoma by partial liver irradiation with doses between 50 and 77 Gy. The tolerance was assessed by the complication probability (Lyman's model), which concerned the injured tissue itself, and by a prediction score used for postsurgical liver failure, which concerned the preserved functional capacity, assuming that the $\geqslant$30 Gy volume was equivalent to the resected volume. The prediction score corresponded better with the observed risk of fatal liver failure than the complication probability. The liver volume after radiotherapy correlated largely with the untreated volume and the low-dose volume. Thus the preserved functional capacity gives a better expression of the radiation tolerance than direct measures of the extent of injured tissue.

Radiotherapy of liver tumors has long been confined to palliative treatment, since the tolerance dose after irradiation of the whole liver is as low as 30 to 35 Gy (1, 2). However, after radiotherapy of tumors in the lower esophagus or the lower part of the lungs, the patients usually do not manifest clinical signs of radiation liver injury, even though a part of the liver is irradiated with high doses. This suggests that the radiation tolerance of the liver is closely related to the volume factor and determined primarily by the preserved functional capacity rather than by the injured tissue itself.

With this hypothesis we applied precisional radiotherapy to hepatocellular carcinomas that partly remained viable after transarterial chemoembolization therapy (3). The radiation fields were $10 \times 10\ cm^2$ or smaller and the target doses were escalated from 50 Gy up to 81 Gy in this pilot study. All the 15 patients who entered the study, most of them with liver cirrhosis, survived more than 6 months after radiotherapy and 12 patients survived more than 19 months. Routine biochemical liver function tests as GOT, bilirubin, and alkaline phosphatase certainly revealed more or less impairment of the liver function. However, these tests could not be used for estimation of the radiation tolerance as the liver function was already impaired to various degree by cirrhosis or affected by the chemoembolization therapy. Moreover, these tests relate mainly to the injured tissue itself and not to the preserved functional capacity.

Since the liver is a functionally homogeneous organ, the preserved functional capacity can be assumed to be proportional to the volume of undamaged liver tissues. On follow-up computed tomographic (CT) scans, we observed that the liver decreased in volume after radiotherapy mostly due to shrinkage of the treated part. Thus, the liver volume after radiotherapy consists largely of the untreated parts where the functional capacity should be preserved. These volumes can be estimated with a dose–volume histogram analysis (DVHA). In the present study we have analyzed if the preserved functional capacity can serve as a major determinant for the radiation tolerance of the liver.

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Table 1

Patient profiles and radiotherapy items

Pat. No.	Age/Sex	Liver function ICG R15(%)	Dose Gy/F/D	Portal	
				Direction	Initial size (cm)
1	60/M	32.0	50.0/25/37	A*, R*	8 × 6 × 6
2	83/M	4.0	55.0/25/33	A, R	9 × 10 × 10
3	55/M	56.0	59.4/33/49	A, R	4 × 4 × 4
4	55/M	48.0	59.4/33/50	R-O*, L-O*	8 × 6
5	65/M	15.5	66.0/30/47	A, R	6 × 6 × 6
6	58/F	42.0	68.4/38/63	A, P: A*, A-O*	9 × 11
7	71/M	33.0	70.0/35/57	R-O, L-O: A*, R*	9 × 9
8	58/M	35.0	70.2/39/61	A, R	5 × 5 × 5
9	67/M	28.0	70.2/39/53	A, R, P	4 × 5 × 4
10	61/M	39.0	70.2/39/56	P, R	6 × 6 × 6
11	56/M	32.0	72.0/40/77	P, R	6 × 6 × 6
12	60/M	47.0	77.4/43/63	A	6 × 6

All but pat. No. 2: with liver cirrhosis.
ICG R15: the indocyanine green retention rate at 15 min.
A: anterior, R: right lateral, P: posterior, L: left lateral, -O: oblique.
* Shrinking field technique.

Material and Methods

Patients and treatments. Twelve patients (11 males and one female) with hepatocellular carcinoma treated between January 1987 and July 1991 were included in the study (Table 1). Their ages ranged between 55 and 83 years. All but one patient (No. 2) had liver cirrhosis. Three patients were excluded from the study as they had extensively multiple tumors from the beginning and/or were reirradiated for recurrence; these patients died from different causes 6.5, 11, and 36 months after initiation of radiotherapy. All the patients received chemoembolization therapy with mitomycin C and Lipiodol before radiotherapy, and three patients (Nos. 1, 5, 9) underwent surgical resection of a tumor as well; only microscopic tumor cells left behind in patient No. 5. Four patients (Nos. 1, 6, 9, 10) had multiple tumors among which the largest was submitted to radiotherapy. The tumors submitted were located in the right lobe in all but one patient (No. 12). The treatment volume was determined referring to radioopaque Lipiodol trapped in the tumor or metal clips inserted in the tumor as markers. In order to reduce the treatment volume, we employed non-coaxial portal arrangement basically, a shrinking field technique when possible, and a respiration-gated irradiation technique (4); this technique was also useful in evaluating the actual dose-volumes. The portals were checked by CT scanning with the patient in irradiating position (Fig. 1) and verified by portal film made by the treatment beam. The bowel and the kidneys were completely outside the treatment beams, but a part of the stomach and the lungs were occasionally included in one of the portals. The tumors were irradiated with 6 MV x-rays and the initial portal size ranged between 5×5 cm^2 and 10×10 cm^2. The prescribed total dose ranged between 50.0 Gy/25 f./37 days and 77.4 Gy/43 f./63 days. Ten patients underwent another chemoembolization therapy during and/or after radiotherapy. So far, 6 patients have died of liver failure with progressive multiple tumors 9 to 30 months after initiation of radiotherapy. The remaining 6 patients are still alive with or without disease after observation periods of between 19 and 46 months.

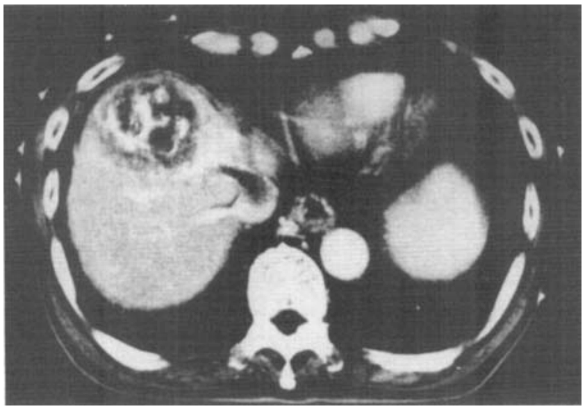

Fig. 1. A postcontrast CT scan of patient No. 7 for the treatment planning. The tumor is seen with Lipiodol trapped after chemoembolization therapy.

Analysis. DVHA and liver volumetry were performed with the computer, Modulex, CMS. By use of the computed cumulative dose-volume histograms, the total liver volume (TLV) was divided into four components of volume with dose range (Gy volume: GV) (Fig. 2). The ranges of dose were supposed to cause functional injury as follows: 1) <10 Gy (no or negligible injury), 2) 10–30 Gy (minor injury), 3) 30–45 Gy (major injury) and 4) $\geqslant 45$ Gy (complete ablation). The radiation tolerance of the liver

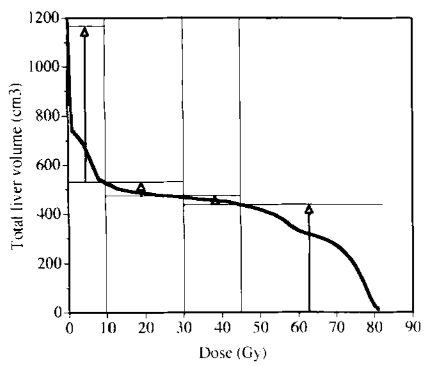

Fig. 2. A cumulative dose volume histogram of patient No. 7 with the liver volume divided into four components according to the radiation doses.

was assessed by the normal tissue complication probability model of Lyman (5), which concerned the injured tissue, and by a prediction score used to estimate safety of hepatectomy in patients with liver cirrhosis (6), which concerned the preserved functional capacity. Equations used for calculation of the complication probability (Pc) of the liver are as follows:

$$Pc = 1/\sqrt{2\pi} \int_{-\infty}^{t} \exp(-t^2/2)\, dt, \qquad [1]$$

where

$$t = (D - TD_{50}(v))/(m^*TD_{50}(v)), \qquad [2]$$

$$TD(v) = TD(1)/v^n, \qquad [3]$$

D is the absorbed dose, $TD_{50}(v)$ the tolerance dose that would result in 50% complication probability for a given partial volume v, TD(v) the tolerance dose for a given partial volume v, TD(1) the tolerance dose for the full volume, and m, n, and $TD_{50}(1)$ are 1.0, 0.40, and 35.0 Gy for the non-cirrhotic, normal liver according to Lyman (5). Equations used for calculation of the prediction score (PS) are as follows:

$$PS = 0.993^*A + 1.12^*B + 0.999^*C - 84.6, \qquad [4]$$

where A is the resection volume rate defined as Eq. [5], B the indocyanine green retention rate at 15 min (ICG R_{15}), and C the patient's age.

$$A = (X - Z)^*100/(Y - Z), \qquad [5]$$

where X is the resected liver volume, Y the TLV, and Z the tumor volume. Score was calculated assuming that the resected volume was equivalent to the $\geqslant$30 GV (PS_{30}) or the $\geqslant$10 GV (PS_{10}). The safe limit of hepatectomy is known to be 50 in score (6). A change of the TLV over 6 months or more after initiation of radiotherapy was studied in 8 patients with the follow-up CT scans available (Fig. 3). The TLV at 6 months (TLV_6) and 12 months (TLV_{12}) after radiotherapy were determined by interpolating the volumetrized TLVs. These periods corresponded

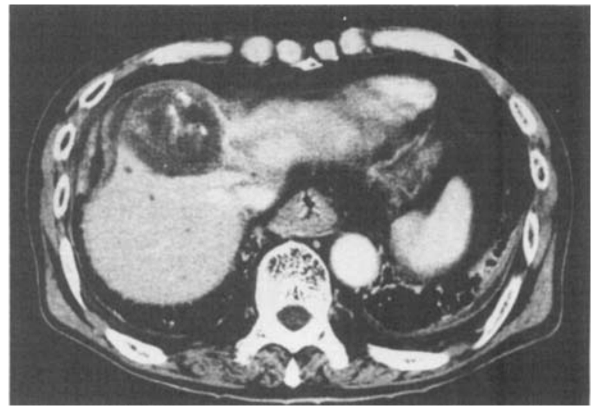

Fig. 3. A postcontrast CT scan of patient No. 7 twelve months after initiation of radiotherapy. Marked volume decrease of the liver tissue surrounding the tumor mass is observable.

with the phase of acute and late injury. Correlation between these parameters was examined: the complication probablity vs. the PS_{30}/the PS_{10} vs. the TLV_6/the TLV_{12}, four components of the GV and another four combined components (< 30 GV, < 45 GV, $\geqslant$30 GV, and $\geqslant$10 GV) vs. the TLV_6/the TLV_{12}. The equations with the variables of the GV were derived by a multiple regression analysis to examine the contribution of each component of the GV to the TLV_6 and the TLV_{12}. Significance of the correlation was determined with the F-test.

Results

The TLV at the treatment planning ranged between 813 and 1 709 cm^3, averaging 1 120 cm^3 (Fig. 4). The cirrhotic livers were much smaller than the non-cirrhotic. The tumor volume ranged between 14 and 239 cm^3, averaging 72 cm^3 and the $\geqslant$45 GV excluding the tumor volume ranged between 25 and 224 cm^3, averaging 115 cm^3 (10.3% of the TLV). Among the other three GV components the < 10 GV was the largest (55.8% of the TLV) on the average followed by the 10–30 GV (22.0%) and the 30–45 GV (5.5%).

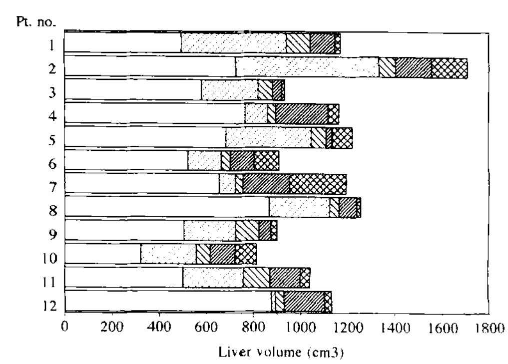

Fig. 4. The components of the total liver volume divided according to the radiation doses. □ < 10 GV ▨ 10–30 GV ▧ 30–45 GV ▩ $\geqslant$ 45 GV ▦ tumor volume.

Table 2

Patients' survival, complication probability and prediction scores

Pat. No.	Survival (months)	CP	PS30	PS10
1	30 DOD	0.003	28.9	67.6
2	31+ NED	0.008	17.0	55.7
3	9 DOD	0.002	43.9	69.8
4	14 DOD	0.969	47.1	55.6
5	23+ NED	0.000	5.5	37.1
6	11 DOD	0.769	37.5	53.9
7	19+ NED	0.991	46.9	54.2
8	36+ NED	0.039	21.8	42.5
9	12 DOD	0.001	30.5	55.6
10	10 DOD	0.365	42.7	74.9
11	46+ AWD	0.473	31.4	56.8
12	29+ NED	1.000	47.0	48.5

DOD: dead of disease, NED: no evidence of disease, AWD: alive with disease.
CP: complication probability.
Prediction scores assuming that the surgical resection volume is equivalent to the $\geqslant 30$ Gy volume (PS_{30}) and the $\geqslant 10$ Gy volume (PS_{10}).

The complication probability ranged between 0.0004 and 1.000 (Table 2). Among four patients with the values 0.769 or higher, who survived 11 months or more, two patients (Nos. 4, 6) died of liver failure but after repeated chemoembolization for subsequently appearing multiple tumors. The PS_{30} ranged between 5.5 and 47.1 and the PS_{10} between 37.1 and 74.9; score was higher than 50 in 9 patients with the PS_{10}.

The TLV changed after the treatments according to the following patterns: 1) immediate increase after chemoembolization, 2) immediate decrease after initiation of radiotherapy, and 3) a late plateau with or without a moderate increase (Fig. 5). Eventually, the TLV_6 in 8 patients and the TLV_{12} in 7 patients decreased on average to 88% and 85% of the TLV at the treatment planning.

The complication probability correlated well with the TLV_6, the TLV_{12}, and the PS_{30}, but not with the PS_{10} (Table 3). Both the TLV_6 and the TLV_{12} correlated well

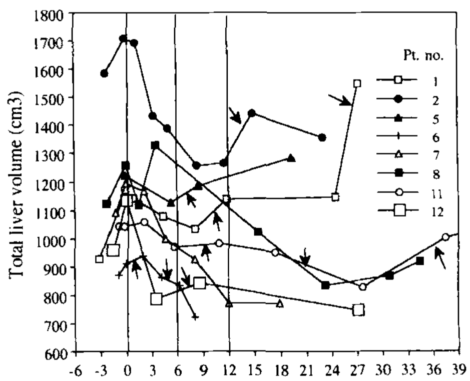

Fig. 5. Change in the total liver volume of 8 patients after the treatments. The arrows indicate chemoembolization therapy performed during and/or after ratiotherapy.

with the components of 10–30 GV, <30 GV, <45 GV. The equations that estimated the TLV_6 and the TLV_{12} were derived as follows:

$$TLV_6 = 529.12 + 0.47{*}V_0 + 0.93{*}V_{10} - 0.82{*}V_{30} + 0.05{*}V_{45}, \quad [6]$$

$$TLV_{12} = 951.16 + 0.03{*}V_0 + 0.97{*}V_{10} - 1.48{*}V_{30} - 0.51{*}V_{45}, \quad [7]$$

where V_0 is the <10 GV, V_{10} the 10–30 GV, V_{30} the 30–45 GV, and V_{45} the $\geqslant$45 GV. Squared correlation coefficient was 0.84 ($p = 0.146$) for Eq. [6] and 0.98 ($p = 0.039$) for Eq. [7]. The coefficient value was largest for the variable 10–30 GV followed by the <10 GV and negative for that of the $\geqslant$45 GV and the 30–45 GV.

Discussion

The radiation tolerance of the partly irradiated liver has not been fully studied. The main reasons for this are: 1) limited experience of radiation liver injury due to dose restriction or to uncommon demands for a high-dose partial liver irradiation and 2) lack of discriminating in-

Table 3

Correlation between the component of liver volume, the total liver volume after radiotherapy, the complication probability, and the prediction score, shown with R2 value

	Component of liver volume (GV: Gy volume)			Prediction score		Complication probability
	10–30 GV	<30 GV	<45 GV	PS30	PS10	
TLV6 (n = 8)	*0.639	**0.783	**0.792	*0.596	0.034	*0.693
TLV12 (n = 7)	**0.870	*0.691	**0.792	**0.838	0.006	**0.905
Complication probability (n = 12)	–	–	–	*0.499	0.008	–

The total liver volume: at 6 months (TLV_6) and 12 months (TLV_{12}) after the initiation of radiotherapy.
The prediction score: Supposed the resection volume was equal to the $\geqslant 30$ GV (PS_{30}) and $\geqslant 10$ GV (PS_{10}).
*: $p < 0.05$, **: $p < 0.01$.

dices for assessing liver injury and preserved functional capacity. With our hypothesis, a patient does not achieve fatal liver failure as long as 'the tolerance functional capacity' is preserved.

This hypothesis fits with the surgical experience. In some equations that estimate the risk of posthepatectomy liver failure in cirrhotic patients (6, 7), the common variables have been the liver resection volume rate or the remaining liver volume and ICG tests, ICG R_{15} and/or ICG Rmax (the maximal ICG removal rate), which appraise functional quality of the entire liver. We used Yamanaka's equation (6) simply because of lack of ICG Rmax data. This equation, however, included the patient's age as a variable which was not included in another equation (7). The patient's age can be a risk factor of extrahepatic complications which could indirectly cause liver failure in surgery, but normally not in radiotherapy. Even with such an equation that heightened the PS value in aged patients, the PS_{30} agreed with the observed risk, all the patients survived at least the phase of acute injury. The PS_{10}, however, highly overestimated the risk. This overestimation implies that the 10–30 GV suffered from only minor or reparable functional injury.

The complication probability, although correlated significantly with the PS_{30}, was as high as 0.769 or more in four patients. While complications do not necessarily imply fatal injury, Lyman's model also probably overestimates the risk, especially in patients treated with higher dose and larger treatment volume, even if cirrhotic livers underwent chemoembolization that should enhance the liver injury as well. The overestimation with this model was also indicated by Lawrence et al. (8). They studied patients with tumors metastasized to the non-cirrhotic liver treated with high-dose partial liver radiotherapy by twice daily irradiations, combined with concurrent intraarterial hepatic chemotherapy. They defined liver injury as at least two-fold anicteric elevation of alkaline phosphatase and non-malignant ascites without progressive disease within four months after completion of treatment. Liver injury developed only among patients treated by total liver irradiation with doses of >37 Gy $\pm$ boost, but not among patients treated by partial liver irradiation alone with doses up to 72.6 Gy even showing higher complication probability values. They managed to solve this problem of overestimation by modifying the value of n in Eq. [3] by employing 0.69 instead of 0.32, while we employed an intermediate value of 0.40.

The normal tissue complication probability model would properly estimate the complication probability for the organs where complications due to radiation injury can be compensated by tissue spared from injury. Therefore, as far as this model is adopted, some modification of the equation would be necessary to solve the problem of this overestimation. However, the overestimation can be interpreted simply as follows: a large increase of the target dose only causes a moderate increase of $\geqslant 30$ GV and $\geqslant 45$ GV, i.e., a moderate decrease of the preserved functional capacity.

In conclusion, our study strongly suggests that the radiation tolerance of the liver can be largely assessed by the preserved functional capacity rather than by expressions for the injured tissue. Refined radiation techniques that preserve the functional capacity as much as possible are essential in order to increase the tolerance.

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