Chinese Journal of Cancer Research 7(2): 130 - 133, 1995.

THE IMPACT OF RADIOTHERAPY COURSE LENGTH ON THE TREATMENT RESULTS OF NASOPHARYNGEAL CARCINOMA (NPC)

Chen Xianzhao 陈显钊 Tang Qixin 唐启信

Department of Radiotherapy, The People's Hospital of Hainan Province, Haikou, 570311

Analyses were made among four radiotherapy schedules for NPC in order to determine whether there is an impact of radiotherapy course length on treatment results.

A series of 320 NPC patients were divided into four radiation treatment branches each with a schedule, this clinical trial was non - randomized. Radiotherapy course length factor was considered with a derivative LQ model formula that biological effective dose (BED) = nd [1 + d/ (α/β)] - k(T - 28). The four branches were: 1. split - course 103 cases, with an intermediary rest of 3—4 weeks, mean total dose 70Gy/35fx, 73d, BED 51.6 Gy; 2. continuous 115 cases, 72Gy/36fx, 61d, BED 62.6 Gy; 3. hyperfractionation I 52 cases, 1.5 Gy b.i.d., time interval (Ti) ≥ 6 hr, 75Gy/49fx, 57d, BED 65.5Gy; 4. hyperfractionation II 50 cases, 1.2 Gy b.i.d., Ti≥6hr, 76Gy/60fx, 59d, BED 63.0 Gy.

Treatment results were compared with 1 - , and 3 - year loco - regional recurrent rates, and 1 - , and 3 - year survival rates, and these rates were of a negative interrelation with prolonged course duration, but of a positive one with BED values. Continuous branch was of a course mean 12 days shorter than the spilt - course one, its treatment results were nearly 10% higher in some subgroups ; and hyperfractionation branches were slightly better than continuous one.

Key words: Radiotherapy couse, Biological effective dose (BED), Nasopharyngeal carcinoma (NPC).

Tumor cells regeneration exists during the whole radiotherapy course, especially an accelerated regeneration presents during the latter segment of the course, which is about four weeks after the start of radiotherapy for epithelially originated carcinoma such as squamous cell carcinoma that most commonly found in NPC. Many clinical trials reported that treatment results were influenced by treatment course length while other treatment conditions were the same. A series of 320 NPC patients treated with their first definitive radiotherapy course in our department were analyzed in order to determine whether there is an impact of treatment course length on their treatment results, and the course length factor was considered with a derivative LQ model formuls.[1]

MATERIALS AND METHODS

This series of 320 patients were of histo -

Accepted January 10, 1995

pathologically proven NPC, and were treated with their first definitive radiotherapy course at our department from Jun 1988 to Sep 1990. The patients were aged 15—76 years old (mean 58 y), the male to female ratio was 3.4 : 1. All patients were staged after CT scanning, and followed the Changsha Staging System (1979). The split - course schedule was applied before 1990, and after its disadvantages were discussed extensively, the routine radiotherapy schedule has been changed to a continuous one since 1990. A non - randomized hyperfractionation clinical trial (hyperfractionation Ⅰ) was in progress in 1990, and it was then changed to another hyperfractionation schedule (hyperfractionation Ⅱ) because of higher oral mucosal and skin reaction rates. Unplanned interruptions were met within continuous and hyperfractionation courses not uncommonly because the patients' tolerance was not quite good, and radiation leukopenia, dermatitis, and complicated oral fungal infections were main causes, but generally, those unplanned interruptions were less than two weeks in a sum for each case who had in the continuous branch.

The biological effective dose (BED) was calculated with a derivative LQ model formula that $BED = nd[1 + d/(\alpha/\beta)] - k(T - 28)$, in which $nd = D$, the total dose; α/β ratio is 10 Gy for carcinoma that mostly squamous cell carcinoma; T is the radiotherapy course length in days, $k = 0.6$ Gy $(1 + 2/10) = 0.72$ Gy (BED) for treatment course length every one day beyond four weeks; and the incomplete recovery of SLD at the time interval between irradiation fractions of hyperfractionation on daytime was neglected in this formula.

The four radiotherapy schedules in this series were: 1. split - course 103 cases, 2.0 Gy/fx, and 5 fx/week, with an intermediary rest of 3—4 weeks, mean total dose 70Gy/35fx, 73d, BED 23.7—67.9 Gy (mean 51.6 Gy); 2. continuous 115 cases, 72Gy/36fx, 61d, BED 42.0—76.1 Gy (mean 62.6 Gy); 3. hyperfractionation Ⅰ 52 cases, 1.5 Gy b.i.d., time interval (Ti) ≥6 hr on daytime, 75Gy/49fx, 57d, BED 48.5—82.3 Gy (mean 65.5 Gy); 4. hyperfractionation Ⅱ 50 cases, 1.2 Gy b.i.d., Ti ≥6 hr, 76Gy/60fx, 59 d, BED 43.0—84.7 Gy (mean 63.0 Gy).

This series of patients have been followed - up for at least three years, 55 cases who lost of follow - up within three years were considered as dead from the month of the last follow - up, and the rate of follow - up was 83%.

RESULTS

The treatment results of this series were listed and analysed in Tables 1 - 3.

DISCUSSION

It has well been recognized that the clonogenic tumor cells may regenerate vigorously during radio -

Table 1. Relations between radiotherapy course length in days and 1 - , and 3 - year loco - regional recurrent rates, and 1 - , and 3 - year survival rates of the present series.

Course length (days)	≤60		61 -		71 -		≥81	
No. of cases' %	137	%	85	%	62	%	36	%
R1	19	13.8*	21	24.7	18	29.0*	11	30.5
R3	45	32.8**	38	44.7	32	51.6**	28	77.7
S1	121	88.3†	68	80.0	42	67.7†	23	63.8
S3	85	62.0††	49	57.6	26	41.9††	12	33.3

R1: 1 - year loco - regional recurrent rate S1: 1 - year survival rate
* $u = 2.35$ $P < 0.05$; ** $u = 2.25$ $P < 0.05$; † $u = 3.1$ $P < 0.01$; †† $u = 2.6$ $P < 0.01$.

Table 2. Comparisons of treatment result with lesion regression and survival rates in the four treatment branches of the present series.

Schedules	BED(mean)	CR	%	PR	%	S_1	%	S_3	%
Split – course	51.6Gy	60/103	58.3*	39/103	37.8	76/103	73.3**	48/103	46.6
Continuous	62.6Gy	76/115	66.1	36/115	31.3	89/115	77.4	64/115	55.7
Hyperfra – Ⅰ	65.5Gy	35/52	67.3	16/52	30.8	44/52	84.6	31/52	59.6
Hyperfra – Ⅱ	63.0Gy	40/50	80.0*	10/50	20.0	46/50	92.0**	29/50	58.0

CR: complete regression; PR: partial regression

* $u=2.2$ $P<0.05$ ** $u=3.2$ $P<0.01$

Table 3. Relations between radiotherapy course length and survival rates in the four stages of the present series

Course	Length (days)	≤60		61 –		71 –		≥81	
stage	No. of cases	S_1%	S_3%	S_1%	S_3%	S_1%	S_3%	S_1%	S_3%
Ⅰ	2			100	100				
Ⅱ	62	93.8	78.7	94.4	77.8	85.7	71.4	80.0	60.0
Ⅲ	131	85.7	49.2	80.0	65.0*	85.7	50.0	78.6	35.7*
Ⅳ	125	67.2	50.9	72.0	52.0**	70.4	33.3	66.7	23.5**

* 26/40; 5/14; $u=1.97$ $P<0.05$ ** 13/25; 4/17; $u=1.99$ $P<0.05$

diotherapy course. Gap in treatment schedule which lead to prolongation of overall treatment time may therefore cause sparing of tumor, and lowering loco-regional control and survival rates. Comparisons of treatment results between split – course and continuous schedules for nasopharyngeal carcinoma were good examples, because the sole difference between two schedules was whether or not there was an intermediary rest of 3—4 weeks. Most of the clinical reports indicated that local control and survival were poorer for patients treated with split – course technique,[2-5] and compensating solutions must be applied after a gap to keep treatment results not declined. In the present series, treatment results were compared with 1 – , and 3 – year locoregional recurrent rates, and 1 – , and 3 – year survival rates, and these rates were of a negative interrelation with prolonged course duration. Continuous branch was of a course mean 12 days shorter than the split – course one, its treatment results were nearly 10% higher in some subgroups; and hyperfractionation branches were slightly better than continuous one.

The derivative LQ model formula, which is with a number of radiobiological parameters that based on a great deal of experimental and clinical data, can effectively demonstrate quantitative analyses of treatment results for different schedules with special consideration of treatment course length, it was referred in the analyses of the present series, and it indicated that treatment results were of a positive interrelation with BED values, implying a negative one with prolonged treatment course which was confirmed in the present series.

Saunders et al.[6] introduced a continuous, hyper-fractionated, accelerated radiotherapy (CHART) for patients with non – small cell carcinoma of the bronchus, which were 50.4Gy/36 fx, 12 d, and 54 Gy/36 fx, 12 d, sequently, the BED of which to squamous cell carcinoma were

57.5 Gy and 62.1 Gy, respectively. Treatment results were superior to a previous trial of conventional 60 Gy/6w (BED 61.9 Gy) schedule with a radiosensitizer, which cause was that the treatment course of the former was much shorter, and CHART also succeeded in treating head and neck carcinomas. Herskovic et al.[1] modified the CHART schedule to a hyperfractionated accelerated one with 79.2 Gy/72 fx, 32 d, in 24 treatment days, with all fractions delivered during normal working hours, its BED was 85.0 Gy; while incomplete repair of SLD after a time interval of 6 hr on daytime was also considered, its BED = 86.2 Gy, treatment results were superior to those with a conventional one of 70Gy/7w, BED = 68.9Gy.

Lindstrom et al.[7] also stressed the influence of overall time on local control in radiotherapy, they used of logistic regression for a re - analysis of local control in a series of 310 T3, T4 squamous cell carcinoma of the larynx and previously published data, a larger effect of overall time was found than in the original publication, but their Model B: logit (probability of local control) did not consistent with the clinical results of our series so well as Herskovic's formula did.

The analyses of the present series made a further confirm of the importance of radiotherapy course length on the treatment results, and the derivative LQ model formula seems available for optimizaiton and outcome prediction for radio - therapy schedules.

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