

A CLINICAL STUDY ON INTRALUMINAL HYPERTHERMIA COMBINED WITH EXTERNAL IRRADIATION FOR ESOPHAGEAL CARCINOMA

Wang Jianhua 王建华 Li Dingjiu 李鼎九

Henan Tumor Hospital, Zhengzhou, Henan 450003

A randomized trial of intracavitary microwave hyperthermia combined with external irradiation (R+H) versus radiation (R) alone in the treatment of esophageal cancer was performed from February 1986 to February 1988. In the R group, radiation was given by 8 MV X-ray with 2 Gy/fraction, 5 fractions per week with a total dose of 60 Gy/6 weeks. In the R+H group, the radiation was given as R group but with a total dose of 40 Gy/4 weeks. Intracavitary 915 Mhz microwave hyperthermia was given with a nominal temperature of 43.5 °C at the margin of the tumor surface, 45 minutes/session, 1-2 sessions/week for 4-8 session. The 1-, 3-, and 5-year survival rates in R+H group were 81.2% (48/59 cases), 42.4% (25/59) and 23.7% (14/59), while in the R group 59.0% (39/66 cases), 24.2% (16/66) and 16.7% (11/66) respectively. The differences in 1- and 3-year survival rates were statistically significant ($P<0.05$) between the 2 groups. Using the thermal dose T90 analysis, after the cases with T90<43 °C (insufficient thermal dose) were eliminated, 52 cases with T90 equal to or higher than 43 °C had 1, 3, and 5 year survival rates of 84.6%, 44.2% and 26.9%, respectively. Statistically significant differences in the 2 groups were also limited only to 1- and 3-year survivals. Higher 5-year survivals is anticipated if more cases are studied.

Key words: Esophageal neoplasms, Radiotherapy, Microwaves hyperthermia.

The cell radiosensitivity, especially the S-phase cells and anoxic cells, may be enhanced at elevated temperature; while combined hyperthermia with radiotherapy may raise the rate of local control over tumors.¹ From February 1986 through February 1988, a prospective study was conducted on intraluminal hyperthermia combined with external irradiation in the treatment of cancer of the esophagus. At random, cases were divided into 2 groups; the group undergoing external radiation plus intracavitary microwave hyperthermia (R+H) and the group given external radiation alone (RT). The aim of this study was to further evaluate the value of the R+H approach in the treatment of esophageal carcinoma.

MATERIALS AND METHODS

Clinical Data

The total patients of the 2 groups numbered 125, all being under 65 in age. The length of the esophageal lesion was ≤ 7 cm. All the cases were diagnosed through barium meal radiography plus pathology/cytology. All the cases having been followed up for over 5 years and with a 94.4% rate of follow-ups. Statistically, those who missed the post-treatment investigation were regarded as deaths at the last message. Table shows the randomly grouping conditions of the 2 groups. The basic information of these 2 groups was basically the same.

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Table 1. Basic data on R+H and RT groups

	R+H		RT	
	Cases	%	Cases	%
Male	36	61	36	55
Female	23	39	30	45
Age (year)	37-65		36-65	
Averaged age	51		51	
Site of lesion				
Upper third	13	22	15	23
Middle third	45	76	48	73
Lower third	1	2	3	4
Lesion length (cm)				
≤5	38	63	44	59
>5	21	37	22	41
Clinic-pathological type				
Medullar type	52	88	57	86
Fungating type	7	12	8	12
Others			1	2
Total	59		66	

Methods of Treatment

For the R+H Group

Intracavitary hyperthermia was given by a 915 MHz microwave unit with the esophageal microwave applicator designed by our laboratory. Three thermocouples were located on the surface of the applicator at the center, 3 cm and 5 cm toward the cable side measuring the temperature at the center of the tumor surface, the margin of the tumor and the normal tissue. They were named as T0, T3 and T5. The temperature curves were plotted by a recorder simiautomatically. It was required that the temperature at the tumor center and its margin have a ≥ 43.5 °C, and the normal tissues have a < 43.5 °C.

Hyperthermia was given 30-60 min. post irradiation for 45 minutes/session. Time-count began when T3 reached 43 °C. Hyperthermia was given 1-2 sessions per week, while the whole treatment course was composed of 4-8 sessions. The effective heating length of the applicator was 9-10 cm. For the patients in R+H group, radiation was given through AP and PA fields. The dose was 2 Gy/session, 5 sessions per week. The total dose was 40 Gy/4 week.

For the RT Group

Radiation was given through one anterior AP port and two posterior oblique ports by 2 Gy/session/day to a total dose of 60 Gy/6 weeks.

RESULTS

Short-term Results

Within one month after treatment, esophageal barium-meal Z-ray film was taken to evaluate their short-term effects. The Grade I response seen in the R+H group was 46.0% compared to 24.0% achieved in the RT group ($P < 0.05$).

Survival Rates

Table 2 shows the survival rates of both groups. The 1-yr, 3-yr and 5-yr survivals in the R+H group were superior to those of the RT group; while the 1-yr and 3-yr survivals were of statistical significance ($P < 0.05$).

Length of the Lesions

According to the length of the lesions, the patients were divided into 2 groups — the ≤ 5 cm and the > 5 cm group. Table 3 and Table 4 show the survivals of them respectively. The survivals of the ≤ 5 cm group in Table 3 were all superior to those observed from Table 4 through R+H treatment. The 1-yr, 2-yr and 3-yr survival rates were of statistically significant ($P < 0.05$); while no such significance is shown from the > 5 cm group ($P > 0.05$).

Local Control

Of the 59 cases in the R+H group, each of the 55 cases had a complete thermal chart. When the average T90 < 43 °C cases were excluded, there remained 52 such cases. Using ≥ 36 months of survival period as a local control level, local recurrence within 36 months would be regarded as such. If cases had a distant metastasis but showed no signs of local recurrent, they were also considered as belonging to the local-control category. The above criteria was used as a means to evaluate the relationship between

hypothermic quality and local control. Table 5 shows number of hyperthermic sessions and local control. The patients were divided into 3 groups. As shown from this table, there was no direct relations between hyperthermic sessions and local control.

Survival Rates in Different Groups

As shown in Table 6, the 5-yr survival rate of R+H group might be raised to 26.9% when cases having T90 ≥ 43.5 °C in comparison with the cases

receiving RT alone, who had a survival rate of 16.7%. As such specimens were fewer in number, the difference was not significant ($P > 0.05$).

The Causes of Death

Local recurrence was the main cause of failure in both groups. The R+H group had a 88.9% of local recurrences, while the RT group 87.9%. The distant metastases occurring in both groups were 11.1% and 12.7% respectively.

Table 2. 5-year survival rates of the R-H and RT group

Group	Cases	1-yr		2-yr		3-yr		4-yr		5-yr	
		Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
R+H	59	48	81.2	35	54.2	25	42.4	18	30.5	14	23.7
RT	66	39	59.0	22	33.3	16	24.2	15	22.7	11	16.7
<i>P</i>		<0.05		<0.05		<0.05		>0.05		>0.05	

Table 3. Survival after R-H and RT in the ≤ 5 cm group

Group	Cases	1-yr		2-yr		3-yr		4-yr		5-yr	
		Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
R+H	38	34	89	25	66	20	53	16	42	13	34
RT	44	28	64	16	36	10	23	10	23	8	18
<i>P</i>		<0.05		<0.05		<0.05		>0.05		>0.05	

Table 4. Survival after R-H and RT seen in the ≤ 5 cm group

Group	Cases	1-yr		2-yr		3-yr		4-yr		5-yr	
		Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
R+H	21	14	67	7	33	5	24	2	9	1	4
RT	22	11	50	6	27	6	27	5	23	3	14
<i>P</i>		>0.05		>0.05		>0.05		>0.05		>0.05	

Table 5. Relation between hyperthermic session and local control

Sessions	Long survival	Metastasis	Relapse	Total	%
3-4	4		5	4/9	44
5-6	10	1	9	11/20	55
7-8	9	2	12	11/23	48

Table 6. Survivals after T+H and RT seen in the ≤ 5 cm group

Group	1-yr		2-yr		3-yr	
	Cases	%	Cases	%	Cases	%
R+H T90 <43 °C	3/3	100	0/3	0	0/3	0
T90 ≥ 43.5 °C	45/52	86.5	23/52	44.2	14/52	26.9
R+H (whole group)	48/59	81.2	25/59	42.4	14/59	23.7
RT	39/66	59	16/66	24.2	11/66	16.7
<i>P</i>	<0.05		<0.05		>0.05	

DISCUSSION

The rationale for combined hyperthermia and radiation in tumor treatment lies in the fact that the radiosensitivity of S-phase cells may be raised at elevated temperature. In addition, hyperthermia can inhibit the repair of the sublethal damage from radiation to the tumor cells.¹

Hou et al.² reported that the results of radiothermo-chemotherapy on esophageal cancer showing that 5-yr survival rate obtained from the triple-therapy was 28.2%, in contrast to 20% from radiation alone. This explains the fact that radiotherapy and chemotherapy combined with hyperthermia may raise local control rate. Findings from our series indicated that intraluminal hyperthermia plus radiation could raise the rate of local control in esophageal cancer. The short-term effect of the R+H group was also superior to that from the RT group, which was of statistical significance. The long-term survival rate of the R+H group was higher than that of the RT group with statistical significant in the 1-yr and 3-yr survival rates. The 5-yr survival rate was 23.7% in R+H group, which is higher than that of the RT group by 16.7%. This is close to the 22.2% of the 5-yr survival reported by Wang et al.³ for their R+H group. In the group having a < 5 cm length of lesion, the results from the R+H group were better than those from the RT group with the 1-yr and 3-yr survival rates having statistical significance. The 5-yr survivals in both groups were 34% and 18% respectively ($P > 0.05$). If the number of cases had been large, possibly, more encouraging results may have emerged.

In the R+H group, the radiation dose was 2/3 of that given by the RT group; therefore the duration of treatment had also been shorter. In the process of treatment, we considered that the key problem lies in

the amount of the thermal dose. As shown from Table 6, not a single case could have survived over 3 years when T90 < 43 °C (3 cases). In a separate paper, discussion was made about the elevation of the local control rate over the tumor happening with the increase in T90. In cases having T90 ≥ 43 °C, the 5-yr survival rate may be as high as 26.9%, apparently higher than 16.7% seen in the RT group. Judging from these findings, it may be held that during hyperthermia, try to raise the temperature within the tumor, if possible at all. The minimum temperature should be T90 ≥ 43 °C. If the temperature could be elevated, the local control rate over the tumor will correspondingly be higher.

Dewey⁴ pointed out that when the patients treated with hyperthermia combined with radiation, adequate amount of thermal dose is needed. In their study on the interstitial hyperthermia for soft-tissue sarcoma Oleson, et al.⁵ pointed out complete dissolution for the soft-tissue sarcoma may be raised to 60% from 35%, when the T90 was raised from 39.5 °C to 41.0 °C. Throughout the whole process of treatment, no apparent correlation was found between the number of hyperthermia sessions and the rate of local control. In their study on the relation between the thermal-dose and tumor local control, Oleson, et al.⁵ pointed out there was only a 5%–8% difference in CR between the weekly 1 and 2 sessions of hyperthermia and the total sessions numbering 2 and 6. We are of the opinion that hyperthermia once a week will be enough. The level of local control rate hinges upon the hyperthermic quality at each session. To better the quality of hyperthermia, do not recklessly change the structure of the applicator and the position of the thermal couple. Instead, the applicator should be periodically corrected.

As shown from this data, the main cause of

death is local recurrence in both groups. While the local control rate of the R+H group was higher than that in the control group. However, the rate of distant metastasis of the R+H group was not higher than that of the RT group. During hyperthermia, the patients didn't complain of any apparent malaise. The slight uncomfortable feeling could be tolerated. The radiation myelitis was not found in both groups.

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