Combination Therapy of Gastric Carcinoma with Radiation and Chemotherapy

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ASAKAWA, H., OTAWA, H., YAMADA, S. and MATSUMOTO, K. *Combination Therapy of Gastric Carcinoma with Radiation and Chemotherapy*. Tohoku J. exp. Med., 1982, **137** (4), 445-452 — The concurrent combination therapy of radiation and chemotherapy was performed in a total of 134 cases of stomach cancer. Radiation response of tumor was remarkable in 35 (37%) of 95 cases, irradiated more than 5,000 rad. Yearly survival rates in 81 cases, in which the scheduled curative treatment was completed, were 63% in one, 31% in two, 21% in three, 17% in four and 13% in five years. These rates were intimately correlated to tumor size and cancer type. However, this combination therapy accompanied some fatal complications in a few percent. From the results, it was concluded that this combination therapy should be valuable to prolong the life of patients with gastric cancer, and that the curable indications for this treatment should be T1-T3; M0 cases with radio-responsive tumor. — radiotherapy; chemotherapy; gastric carcinoma

Gastric carcinoma is the most frequent one in Japan. In the treatment of gastric cancer the curable possibility is only expected by curative resection of the stomach. However, locally unresectable and medically inoperable cases are not rare, in spite of a remarkable progress of the diagnostic method for gastric carcinoma. For such cases in which gastrectomy is not indicated, chemotherapy is generally employed to prolong the life of a cancer patient, but its effect is greatly limited.

On the other hand, the radiation therapy of gastric cancer has been thought to be inadequate, because of relative radioresistance of gastric carcinoma and of the limited radiotolerance of adjacent organs, such as the small intestine, large bowel and kidneys.

Since 1967, we have been trying the concurrent combination therapy of gastric carcinoma with 6 MV x-ray and some anticancer drugs to potentiate the radiation effect on the malignant lesions within the irradiation field. In this therapy, it is expected that chemotherapy alone may be also effective on the subclinical invasions and/or apparent remote metastases in the outside of the irradiation field.

In this study, radiation response of tumor, yearly survival rates and

complications are analyzed and discussed from some clinical points, to evaluate this combination therapy of gastric carcinoma.

MATERIALS AND TREATMENT

From 1967 to 1978, 134 cases of gastric carcinoma were given the combination therapy with radiation and chemotherapy at Department of Radiology, Miyagi Seijinbyo Center (including one case treated by radiation alone). In all cases, adenocarcinoma of the stomach was confirmed by the histologic examination of the specimens of endoscopic biopsy. They consisted of 81 males and 53 females in the age from 28 to 84 years (66.1 years old on the average). By TNM classification of malignant tumors (UICC 1978), they were classified into 13 (10%) of T1, 21 (16%) of T2, 59 (44%) of T3 and 41 (31%) of T4, and in 38 (28%) of them, remote metastases (M1) had been noticed already before the start of this treatment. By cancer type according to "the general rules for the gastric cancer study in surgery and pathology" (Japanese Research Society for Gastric Cancer), they were classed to 13 (10%) of 0 type (early carcinoma), 22 (16%) of I type (tumorous type), 29 (22%) of II type (ulcerous type), 53 (40%) of III type (ulcerous type with marked infiltration), 16 (12%) of IV type (scirrhous type) and one (1%) of V type (unclassified type).

Six MV x-ray generated from a medical linear accelerator was used in radiation therapy. All cases were irradiated through two opposed portals and a total tumor dose of 5,000 rad was planned as the minimum. The dose fractionation was 200 rad/day five times a week in 38, 250 rad/day four times a week in 62, and 400–500 rad/day twice a week in 34 cases. A relatively small irradiation field was planned to include the primary lesion and adjacent nodes.

As a rule, chemotherapy was combined concurrently with irradiation in 133 cases except one case treated by radiation alone. In 37 cases, 5-fluorouracil was administered by intravenous drip infusion; 250 mg/day was given for a week before the start of radiotherapy and thereafter 500 mg/day was injected twice a week. In 62 cases, tegafur was given by intravenous drip infusion (800 mg/day), per os (600 mg/day) or per the rectum (750–1,000 mg/day). In the other 34 ones, FAMT (5-fluorouracil 500 mg, cyclophosphamide 200 mg, mitomycin 4 mg and toyomycin 0.5 mg) or FMC (5-fluorouracil 500 mg, mitomycin 4 mg and cytosine arabinoside 20 mg) was done once or twice a week by intravenous drip infusion.

RESULTS

Completion of the combination therapy

Many cases tolerated well this combination therapy. Out of 96 cases (T1–T4: M0), the scheduled radiation therapy with a total tumor dose of more than 5,000 rad was completed in 81 (84%) cases, but it was interrupted in 15 (16%), from such reasons as aggravation of general condition (in six cases), massive bleeding (in six cases), perforation of the stomach (in two cases) and severe radiation syndrome (in one case). Also, out of 38 cases (T1–T4: M1), the scheduled radiotherapy was completed in 26 (68%) and it was withdrawn in 12 (32%) from the above-mentioned reasons. On the other hand, the interrupted rate of chemotherapy was 8% in 37 cases of 5-fluorouracil group, 3% in 62 cases of tegafur group and 53% in 34 cases of FAMT or FMC group. Leukopenia of less than $2,000/\text{mm}^3$ and/or thrombocytopenia of less than $50,000/\text{mm}^3$ were representative, as the main reason of the interruption of chemotherapy.

Radiation response of tumor

Roentgenologic and endoscopic changes of the primary lesion by irradiation were analyzed in relation to tumor size (T-grade) and cancer type, in 107 cases irradiated more than 5,000 rad.

In 12 cases of T1 (0 type), the primary lesion was so small and superficial that it was quite difficult to demonstrate quantitatively these changes of the primary tumor, but the histologic study of endoscopic biopsy materials revealed the complete disappearance of cancer cells in five (42%) of them.

In 95 cases of T2-T4, radiation response of the primary tumor was divided into four grades, based on roentgenologic and endoscopic changes. These grades were as follows:

Grade I; absence of the decrease in size of the primary tumor

Grade II; slight decrease (less than 50%) in size of the primary tumor

Grade III; marked decrease (more than 50%) in size of the primary tumor

Grade IV; almost complete regression of the primary tumor

As shown in Table 1, radiation response of tumor in 95 cases was Grade I in 21 (22%), Grade II in 39 (41%), Grade III in 30 (32%) and Grade IV in five (5%). The marked radiation response above Grade III, judged as effective, was obtained in 14 (70%) of 20 cases of T2, in 18 (39%) of 46 cases of T3 and in three (10%) of 29 ones of T4. The smaller the tumor size, the more remarkable was the response. Radiation response was most pronounced in I type cases with the effective rate of 78%, and this rate was followed by the rate of 35% in type II cases and of 29% in III type ones, but none of IV type cases showed the effective response.

TABLE 1. *Radiation response of tumor*

T & Type	Number of cases	Grade of response				Marked response (III+IV) (%)
		I	II	III	IV	
T2	20	0	6	11	3	14/20 (70)
T3	46	7	21	16	2	18/46 (39)
T4	29	14	12	3	0	3/29 (10)
I	18	1	3	11	3	14/18 (78)
II	26	2	15	7	2	9/26 (35)
III	38	11	16	11	0	11/38 (29)
IV	12	7	5	0	0	0/12 (0)
V	1	0	0	1	0	1/1 (100)
Total	95	21	39	30	5	35/95 (37)

Yearly survival rates

In this paper, cumulative survival rates were calculated by the actuarial method. As seen in Table 2, the yearly survival rates in a total of 134 cases were 46% in one, 20% in two, 13% in three, 10% in four and 8% in five years, and 50% survival month in them was 10 months. In 81 completed cases (T1-T4: M0), survival rates in one, two, three, four and five years were 63%, 31%, 21%, 17%

TABLE 2. *Survival rates in clinical groups*

Group	Number of cases	Survival period (years)					50% survival month
		1	2	3	4	5	
Completed group (T1-T4; M0)	81	63%	31%	21%	17%	13%	15
Interrupted group (T1-T4; M0)	15	27	0	0	0	0	3
Metastatic group (T1-T4; M1)	38	16	5	3	0	0	4
Total	134	46	20	13	10	8	10

TABLE 3. *Survival rates in relation to T and cancer type*

T & Type	Number of cases	Survival period (years)					50% survival month
		1	2	3	4	5	
T1	12	83%	83%	50%	32%	32%	36
T2	15	80	40	33	25	17	21
T3	30	63	30	24	24	16	15
T4	24	42	8	4	0	0	9
0	12	83	83	50	32	32	36
I	14	71	43	35	26	18	18
II	18	69	20	10	10	10	20
III	27	56	18	15	15	7	13
IV	9	22	0	0	0	0	9
V	1	100	100	0	0	0	

and 13%, respectively. In 15 interrupted cases (T1-T4; M0), one-year survival rate was 27% and there was no two-year survival. In 38 metastatic cases (T1-T4; M1), one-year survival rate was very low with the rate of 16%, but three-year survivals were observed in 3%.

Treatment results in 81 completed cases, relating to tumor size (T-grade) and cancer type, are tabulated in Table 3. The cases of T1 (0 type) showed the most favorable results, with five-year survival of 32% and 50% survival period of 36 months. The results in the cases of T2 and T3 were almost the same: the five-year survival rate in the former was 17% and that in the latter 16%. The result was very poor in the cases of T4, with three-year survival of only 4% and no five-year survival. The cases of I type showed relatively better results, with five-year survival rate of 18% and this rate was followed by the rate of 10% in the cases of II type and 7% in the cases of III type. However, in the cases of IV type one-year survival rate was only 22% and there was no two-year survival. Thus, the survival rates were intimately correlated to tumor size (T-grade) and cancer type.

Five-year survivals

Seven cases of five-year survival are summarized in Table 4. In the clinical stage, they were made up of three of T1M0, two of T2M0 and two of T3M0. The primary tumor arose at the cardia in four cases, at the corpus in two and at the

TABLE 4. *Five-year survivals*

Case	Age & Sex	TM & Type	Location	Histology	Radiation (rad/day)	Chemotherapy	Grade of response	Result
1	66 M	T2M0 II	Cardia	Not specified	5,700/26	5-Fu	III	Alive (14 years)
2	59 M	T1M0 0	Antrum	Tubular	5,000/32	(-)	IV*	Alive (14 years)
3	70 M	T1M0 0	Corpus	Tubular	6,000/50	Tegafur	IV*	Died (6 years)
4	72 M	T3M0 I	Cardia	Papillary	6,000/57	Tegafur	IV	Died (5 years)
5	74 M	T2M0 I	Cardia	Tubular	6,000/41	Tegafur	III	Alive (5 years)
6	72 M	T3M0 III	Cardia	Tubular	6,000/41	Tegafur	III	Alive (5 years)
7	71 F	T1M0 0	Corpus	Tubular	6,250/58	Tegafur	IV*	Alive (5 years)

* Complete disappearance of cancer cells was histologically confirmed in biopsy materials.

antrum in the other. In cancer type, three cases were 0 type, two I type, one II type and the other was III type. Histologic type was tubular adenocarcinoma in five cases, papillary adenocarcinoma in one case and not-specified adenocarcinoma in the other. Total tumor dose ranged from 5,000 rad/32 days to 6,250 rad/58 days. Chemotherapy was concurrently combined in six cases; tegafur was administered in five and 5-fluorouracil in the other. One case was treated by radiation alone. Radiation response of tumor was grade III in three cases and Grade IV in four cases. Five cases are now alive without any evidence of recurrence or remote metastasis, from five to 14 years after the completion of the combination therapy. One case died at six years from acute pneumonia and the other terminated fatally at five years and two months from myocardial infarction.

Complications

Complications by radiation therapy were divided into the early and late types.

As early complications, radiation gastritis, massive bleeding and perforation of the stomach were representative. Radiation gastritis occurred without exception, whenever the irradiated dose exceeded 3,500 rad. Endoscopic examination revealed edema, erosion and small hemorrhagic foci on mucosa of the stomach, with symptoms such as anorexia, gastric pain, nausea and vomiting. If the symptoms were severe, a pause of radiation therapy was necessary for about three weeks and it was actually interrupted in 65 (61%) of 107 cases, irradiated more than 5,000 rad. Massive bleeding from the cancerous lesion was found in nine (6.7%) of 134 cases. The irradiated dose at the occurrence was 1,750 rad/11 days to 6,000 rad/73 days. Further continuation of radiotherapy was possible after the short pause in three cases, but it was impossible in six cases. Perforation of the stomach occurred in two (1.5%) of 134 cases and the irradiated dose at the occurrence was 4,500 rad/28 days and 6,000 rad/43 days. These cases terminated fatally from

this complication. Also, the latter two complications were only observed in the cases of ulcerous type carcinoma (II or III type).

Late complications included hemorrhagic gastritis, chronic ulcer of the stomach and radiation necrosis of the transverse colon. Out of 107 cases, irradiated more than 5,000 rad, chronic ulcer of the stomach developed in four (3.7%), hemorrhagic gastritis occurred in two (1.9%), and radiation necrosis of the transverse colon was found in another (0.9%). These late complications occurred two to six months after the completion of radiation therapy and these cases of late complications were irradiated 6,000 rad or more. A case of hemorrhagic gastritis and another of necrosis of the colon died from these complications.

DISCUSSION

A few five-year survivals have been reported in the literature concerned with radiation therapy of gastric carcinoma (Brandl 1952; Sauerbery and Reihold 1963; Okawa et al. 1976; Wieland and Hymmen 1970). But, it has been generally accepted that eradication of gastric cancer is quite difficult with radiation alone, and that the curative possibility of radiation therapy is remote. To obtain a permanent cure of gastric cancer by radiation therapy, firstly all malignant lesions must be completely included in the irradiation fields, and secondly cancer cells must be eradicated by irradiation. At present, these requirements cannot be fulfilled, because of the uncertainty in diagnosis of lymph node metastases, the low radiosensitivity of gastric adenocarcinoma and the serious complications of adjacent organs.

With the progress of chemotherapy, some trials of the concurrent combination therapy with radiation and chemotherapy have been performed for inoperable gastric carcinoma (Childs et al. 1968; Asakawa and Takeda 1973; Kitagawa et al. 1974, 1975). In such combination therapy, it is reasonable to expect that radiation response of tumor may be intensified by the use of anti-cancer drugs, and that subclinical invasions and/or metastatic lesions in the outside of the irradiation field may be controlled by these drugs alone. If these expectations are sufficiently satisfied, this combination therapy may be chosen as a curative procedure for gastric carcinoma. However, as there has been no report on long-term results of this combination therapy for gastric carcinoma, the limitation, indication, curability and disadvantage of this treatment can be discussed only from the findings in our present study.

From our present data, it was clarified that the histologic disappearance rate of cancer cells in biopsy materials was about 40% even in early carcinoma, and complete regression of tumor was clinically observed in 5% of the cases of advanced carcinoma. Also, it was understood that radiation response of tumor was correlated to tumor size and cancer type, and that long-term survivals were only noticed in the cases which showed a marked radiation response of the tumor. So, the curative possibility of this combination therapy may be greatly limited, like that of radiation therapy alone.

The cases of inoperable carcinoma are divided into three groups; a) the cases for which the curative gastrectomy is not indicated from other medical causes (T1-T3: M0), b) locally unresectable cases (T4: M0) and c) the cases of remote metastases (any T:M1). This combination therapy may be the one and only curative treatment for the medically inoperable group. However, the five-year survival rate in this group, obtained by this combination therapy, is estimated to be about 20% at the highest, and this rate is very low, compared with that obtained by the curative gastrectomy in this center (Yoshida et al. 1977). In many cases of this group, radiation response of tumor is not so remarkable that a permanent cure is hardly expected. However, relative long-term (one to three years) survivals are observed by this combination therapy, except the cases of scirrhous type carcinoma. So, it seems that this combination therapy will be valuable to relieve the subjective symptoms and to prolong the life of a cancer patient with medically inoperable gastric carcinoma. In the cases of locally unresectable carcinoma and with remote metastases, it is unreasonable to expect a permanent cure by any treatment. The present study indicates that three-year survivals are rarely obtained by this combination therapy, and that the results in this therapy are better, compared with the representative results obtained by chemotherapy alone in Japan (Ota et al. 1971; Furue et al. 1974; Yokoyama and Saito 1975). So, it is suggested that this combination therapy will be effective as a palliative procedure for the cases of far advanced gastric carcinoma.

On the other hand, it is said that the tolerance dose of the stomach is about 4,500 rad (1,460 ret), and that if the irradiated dose exceeds this level, complications will occur in a quarter to half of the cases. Also, these complications are thought to be sometimes fatal (Brick 1955; Roswit et al. 1972). In our present results, the incidence of the complications is very low, in spite of the irradiated dose of more than 5,000 rad. It is a serious problem, however, that this combination therapy accompanies fatal complications. As the fatal complications are intimately correlated to cancer type, this combination therapy must be carefully applied in the cases of ulcerous type carcinoma.

References

- 1) Asakawa, H. & Takeda, T. (1973) High energy X-ray therapy of gastric carcinoma. *J. Jap. Soc. Cancer Ther.*, **8**, 362-371.
- 2) Brandl, W. (1952) Die Pendelbestrahlung des Magenkarzinoms. *Strahlentherapie*, **87**, 185-194.
- 3) Brick, I.B. (1955) Effects of million volt irradiation of the gastrointestinal tract. *A.M.A. Arch. intern. Med.*, **96**, 26-31.
- 4) Childs, D.S., Moertel, C.G., Holbrook, M.A., Reitemeier, R.J. & Colby, M. (1968) Treatment of unresectable adenocarcinoma of the stomach with a combination of 5-Fu and radiation. *Amer. J. Roentgenol.*, **102**, 541-544.
- 5) Furue, H., Furukawa, I., Kano, T., Kubo, A., Yokoyama, T. & Nakano, I. (1974) Observations on the life span of advanced cancer cases. *Jap. J. Cancer Clin.*, **20**, 435-440. (Japanese)
- 6) Kitagawa, T., Nakamura, K., Fujii, M., Ishikawa, H., Ito, I., Miwa, K., Kitaoka, H. & Yoshikawa, K. (1974) Radiotherapy with sensitizing drugs to carcinoma of the stomach. *Jap. J. Cancer Clin.*, **20**, 128-135. (Japanese)

- 7) Kitagawa, T., Nakamura, K., Ito, I., Miwa, K. & Doi, H. (1975) Result of radiation therapy combined with FT 207 of inoperable cases with carcinoma of the stomach. *Jap. J. Cancer Clin.*, **21**, 892–896. (Japanese)
- 8) Okawa, T., Nakamura, M. & Kaneta, K. (1976) Results of radiotherapy of inoperable advanced gastric carcinoma 1960 and 1975. *Nipp. Acta radiol.*, **36**, 902–909. (Japanese)
- 9) Ota, K., Kurita, S., Nishimura, M., Ogawa, M., Kamei, Y., Imai, K. & Ariyoshi, Y. (1971) Multiple combination MFC therapy in the chemotherapy of malignancies. *J. Jap. Soc. Cancer Ther.*, **6**, 267–276. (Japanese)
- 10) Roswit, B., Malsky, S.J. & Reid, C.B. (1972) Severe radiation injuries of the stomach, small intestine, colon and rectum. *Amer. J. Roentgenol.*, **114**, 460–475.
- 11) Sauerbery, R. & Reihold, H. (1963) Zur Strahlentherapie des Magenkarzinoms. *Strahlentherapie*, **121**, 193–199.
- 12) Wieland, C. & Hymmen, U. (1970) Megavolttherapie maligner Neoplasien des Magens. *Strahlentherapie*, **140**, 20–26.
- 13) Yoshida, K., Ikeuchi, H., Oshibe, M., Machida, T., Hoshi, H. & Takahashi, M. (1977) Surgical treatment and adjuvant chemotherapy of gastric cancer on the basis of pathological findings. *Tohoku J. exp. Med.*, **122**, 113–120.
- 14) Yokoyama, M. & Saito, T. (1975) Evaluation of cancer chemotherapy from viewpoint of survival of patients with gastric cancer. *Cancer and Cancer Chemother.*, **2**, 367–375. (Japanese)