Radiation Therapy of Carcinoma in the Rectum and Sigmoid Colon

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ASAKAWA, H., OTAWA, H., SAITO, H. and NEMOTO, K. Radiation Therapy of Carcinoma of the Rectum and Sigmoid Colon. Tohoku J. exp. Med., 1984, 144 (4), 409-416 — Radiation therapy combined with some anti-cancer drugs was performed in a total of 79 patients with carcinoma of the rectum and sigmoid colon, consisting of 41 primary, 25 recurrent and 13 postoperatively irradiated ones. Relief of subjective symptoms was observed in 50% or more of primary and recurrent patients. Radiation response of tumor was marked in 23 (56%) of primary ones. Five-year survival rate was 21% in the primary patients without any remote metastasis, 11% in the recurrent and 27% in the postoperatively irradiated. It was concluded that this combination therapy might be valuable for getting a cure in the primary patients with radioresponsive tumor (T1-T4 : M0) and the patients with localized residual lesion, and for good palliation in the patients with far advanced and recurrent carcinoma.

Recently, mortality from colorectal carcinoma has gradually increased in Japan. Owing to great progress of the diagnostic method for this malignancy, early and less advanced carcinomas of the rectum and colon have become detectable. However, locally unresectable and medically inoperable cases of colorectal cancer are not rare.

Surgery and radiotherapy are the two major modalities for the curative treatment of cancer. In the management of colorectal carcinoma, a permanent cure is only expected from curative surgery. Radiotherapy has been considered to have no value for the control of this malignancy. However, some recent studies (Papillon 1975; Syed et al. 1978; Wassif 1983) suggest that such issue is questionable.

Since 1967, the concurrent combination therapy of colorectal cancer with radiation and some anti-cancer drugs have been tried at Miyagi Seijinbyo Center. In this treatment, anti-cancer drugs may intensify the radiation effect on the malignant lesion and they may be effective to control the subclinical invasions and remote metastases.

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In this paper, radiation response of tumor, relief of subjective symptoms and survival rate are analyzed and the role of this combination therapy for colo-rectal carcinoma are discussed.

**Materials and Treatment**

From 1967 to 1983, 79 patients with histologically confirmed adenocarcinoma of the rectum and sigmoid colon were treated with radiation at Department of Radiology, Miyagi Seijinbyo Center. They consisted of 48 males and 31 females in the age from 33 to 87 years (58 years old on the average). They were classified into 3 groups: 41 primary cases, 25 recurrent and/or metastatic cases after surgical treatment and 13 postoperatively irradiated cases following palliative resection of primary tumor.

In the radiation therapy, 6 MV x-ray from a linear accelerator was used as a rule, but according to circumstances, 6 to 20 MeV electron was also used for the treatment of metastatic lesions. By conventional dose fractionation (2 Gy/day, 5 times a week or 2.5 Gy/day, 4 times a week), a total dose of 40 Gy was planned as the minimum and 60 to 70 Gy was given, if possible. In 41 primary patients, two opposite fields were chosen to the whole pelvis, including the primary lesion, internal iliac node and common iliac node. An average total dose of 53 Gy was delivered in this group. In 25 recurrent and/or metastatic patients, the recurrent or metastatic lesion was irradiated with an average total dose of 45 Gy. In 13 postoperatively irradiated patients, the residual lesion after palliative resection was irradiated with an average total dose of 53 Gy.

Chemotherapy, being not systematic, was concurrently combined with radiotherapy in 68 (86%) of 79 patients. Out of them, 54 patients were given a single drug (5-fluorouracil in 14, tegafur in 28, carmofur in 7 and other drugs in 5) and 14 were administered multiple drugs (5-fluorouracil, cyclophosphamide, mitomycin c and toyomycin in 10; 5-fluorouracil, mitomycin c and cytosine arabinoside in 4).

**Results**

**Results in primary group**

Primary tumor was located at the rectum in 40 patients and at the sigmoid colon in one patient. According to TNM classification of malignant tumors (UICC, 1978), 41 primary patients were classed to one (2%) of T1, 10 (24%) of T2, 11 (26%) of T3 and 19 (46%) of T4. Remote metastasis (M1) had been already noticed before the start of treatment in 10 (24%) of them.

Eleven patients were considered to be medically inoperable because of serious complications and the other 30 were judged to be unresectable due to extensive advancement of primary tumor and/or distant metastasis. Before radiation therapy, permanent colostomy was performed in 19 patients (46%), to relieve chronic obstruction of the bowel.

Thirty-seven (90%) of the total patients tolerated well this combination treatment with a total dose of more than 40 Gy. However, radiotherapy was interrupted from aggravation of general condition in three patients and ileus of the small intestine in the other.

Subjective response, which was not easy to evaluate due to individual variations, was remarkable in many cases. Bleeding from tumor disappeared perfectly in 22 (73%) of 30 patients, and full relief of pain was observed in 10
(56%) of 18 patients with severe pain. All patients with marked response received a total dose of more than 40 Gy.

Objective radiation response of primary tumor was analyzed by roentgenologic and endoscopic changes. It was divided into 3 grades as follows:

Grade I: No change in primary tumor and slight decrease (less than 50%) in size of primary tumor

Grade II: Moderate decrease (more than 50%) in size of primary tumor

Grade III: Almost complete regression of primary tumor.

Radiation response of primary tumor was grade I in 15 (37%), grade II in 17 (41%) and grade III in only 6 (15%), and it was unable to evaluate radiation response in three (7%) (Table 1). In general, the smaller the tumor, the more remarkable was radiation response and it was pronounced in Borrmann I and II type. A total dose of more than 50 Gy was necessary to obtain the radiation response above grade II, and the patients with the radiation response of grade III were delivered the dose of 60 Gy or more.

Two patients, having a lesion considered clinically unresectable, received radical amputation of the rectum three months after the completion of radiotherapy with the dose of 60 Gy. Histologic examination of operation materials revealed a few viable cancer cells in fibrous granulation tissue in one patient, and no viable cancer cell in the other. No lymph node metastasis was histologically demonstrated in either of them.

Cumulative survival rates were calculate by actuarial method. The survival rates in 39 cases, except two cases resected after radiotherapy, were 68% in one year, 34% in 2, 16% in 3 and 12% in 4 and 5 (Fig. 1). In 29 cases without any remote metastasis, survival rates in one, 2, 3, 4, and 5-year were 82%, 46%, 21%, 21%, and 21%, respectively. 50% survival month was 15 months in the former and 18 months in the latter (Fig. 2). In 27 cases, in which the planned radiotherapy was completely performed and any remote metastasis had not been noticed before the treatment, 5-year survival rate was 23% and 50% survival month was 20 months.

Out of 2 patients treated surgically after radiotherapy, one patient has survived one year without any evidence of recurrence or metastasis, but the other died from metastases of the liver two years and six months after amputation of the rectum.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Primary tumor (41 cases)</th>
<th>Recurrent tumor (18 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15 (37%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>II</td>
<td>17 (41%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>III</td>
<td>6 (15%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>3 (7%)</td>
<td>4 (22%)</td>
</tr>
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</table>
Radiation syndrome, such as anorexia, nausea, vomiting and diarrhea, was not frequent and mild. Radiation injury to peripheral blood (leucopenia below 2,000/mm³ and/or thrombocytopenia below 50,000/mm³) was not observed except only one patient. Severe complication of the small intestine was noticed in one patient and led him to fatal outcome.

Fig. 1. Survival rates. • •, primary patients (39 patients); ○ --- ○, recurrent and/or metastatic patients (25 patients); △ --- △, postoperatively irradiated patients (13 patients).

Fig. 2. Survival rates. • •, primary patients of T1-4 M0 (29 patients); ○ --- ○, recurrent patients without any remote metastasis (12 patients).
Results in recurrent and metastatic group

In this group, 12 patients had recurrence only, 7 had distant metastasis and 6 had both of them. The irradiated lesions in the recurrent patients were intrapelvic malignancy in 12, perineal infiltration of carcinoma in 4 and local recurrence at the bowel in 2, treated with anterior resection of the rectum. Those in the metastatic patients were bone metastasis of the spine in 5, lymph node metastasis at the paraaortic or left supraclavicular region in 3 and implanted metastasis at the abdominal wall in 2.

Relief of subjective symptoms was observed in 14 (56%) of 25 patients and relief of pain was dramatic in 4 of 5 patients with bone metastasis. Radiation response of recurrent tumor was slighter than that of primary tumor. Radiation response in 18 patients with local recurrence was grade I in 9 (50%), grade II in 4 (22%), grade III in only one (6%) and could not be evaluated in 4 (22%) (Table 1). Lymph node metastasis regressed completely in one, decreased moderately in one and did not change in the other. Irradiation with the dose of more than 40 Gy was necessary to obtain the marked radiation response of recurrent tumor.

Survival rates in this group were 49% in one-year, 22% in 2, 11% in 3 and 6% in 4 and 5. Fifty percent survival month was 10 months (Fig. 1). Survival rates in the patients with local recurrence only were slightly higher and 5-year survival rate showed 11% and 50% survival month was 18 months (Fig. 2). Only one patient with recurrence of the vagina survived more than five years.

Results in postoperatively irradiated group

Postoperative irradiation was carried out to the residual lesions after palliative resection of primary tumor, and it started in one to two months following surgical treatment.

The residual lesions in 11 of 13 patients were the direct infiltration of carcinoma into the neighboring organs, such as the uterus, vagina, urinary bladder, prostate and sacrum. In the remaining two patients, carcinomatous residuum was histologically confirmed at the edge of the resected bowel.

These patients, except one patient, tolerated well radiation therapy and were delivered the dose of more than 40 Gy.

Yearly survival rates in this group were 74% in one-year, 40% in 2 and 27% in 3, 4 and 5. 50% survival month was 21 months (Fig. 1).

Five-year survivals

Seven patients of 5-year survivals are summarized in Table 2. They consisted of 4 primary patients, one recurrent and 2 postoperatively irradiated ones. Primary tumor arose at the rectum in all patients.

In primary cases, the advancement of primary tumor (T-classification) was made up of T1 in one case, T3 in 2 and T4 in the other; lymph node metastasis
was confirmed in 2 cases (each one of N1 and N2), in which permanent colostomy was performed; and any remote metastasis was found in none of them. Cancer type of primary tumor was Borrmann II type in 2 cases, polypoid (early carcinoma) in one and Borrmann I type in the other.

A recurrent patient had carcinomatous infiltration into the vagina, which was histologically confirmed 4 months later after the palliative resection of primary tumor.

The residual lesions in two cases with postoperative radiotherapy were cancerous infiltration into the uterus and urinary bladder.

Histologic type of primary tumor was classed to papillary adenocarcinoma in one patient, papillotubular in 3, tubular in one and poorly differentiated in the other 2.

Irradiated tumor dose ranged from 52.5 Gy/37 days to 70 Gy/64 days. Chemotherapy was concurrently combined in 5 patients; tegafur was administered in 3 and cyclophosphamide in the remaining 2.

Radiation response of tumor, evaluated in 5 patients except the postoperatively irradiated ones, was grade III in 3 patients and grade II in 2, that was almost equivalent to grade III.

Four patients have been now alive without any evidence of this malignancy, from seven to 10 years after the start of radiotherapy. However, one patient has suffered from chronic radiation ulcer of the skin at the perineal region. A recurrent patient died 5 years from carcinomatous peritonitis. A primary patient and the other postoperatively irradiated one, in whom the cause of death could not be traced, terminated fatally. The survival period was 5 years and 3 months in

<table>
<thead>
<tr>
<th>Number</th>
<th>Age/Sex</th>
<th>Stage Type</th>
<th>Histology</th>
<th>Radiation (Gy/days)</th>
<th>Response</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/Male</td>
<td>T4NXM0 B-I</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>70/64 (-)</td>
<td>III</td>
<td>Alive 10 years</td>
</tr>
<tr>
<td>2</td>
<td>71/Female</td>
<td>T1NXM0 Polypoid</td>
<td>Papillotubular adenocarcinoma</td>
<td>60/40 tegafur</td>
<td>III</td>
<td>Alive 8 years</td>
</tr>
<tr>
<td>3</td>
<td>64/Male</td>
<td>T3N2M0 B-II</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>60/42 tegafur</td>
<td>II</td>
<td>Alive 7 years</td>
</tr>
<tr>
<td>4</td>
<td>73/Male</td>
<td>T3N1M0 B-II</td>
<td>Papillotubular adenocarcinoma</td>
<td>52.5/37 tegafur</td>
<td>II</td>
<td>Died 5 years</td>
</tr>
<tr>
<td>5</td>
<td>48/Female</td>
<td>Recurrence (vagina)</td>
<td>Papillotubular adenocarcinoma</td>
<td>60/53 cyclophosphamide</td>
<td>III</td>
<td>Died 5 years</td>
</tr>
<tr>
<td>6</td>
<td>50/Female</td>
<td>Residuum (uterus)</td>
<td>Tubular adenocarcinoma</td>
<td>60/122 (-)</td>
<td>?</td>
<td>Alive 10 years</td>
</tr>
<tr>
<td>7</td>
<td>62/Male</td>
<td>Residuum (bladder)</td>
<td>Papillary adenocarcinoma</td>
<td>? cyclophosphamide</td>
<td>?</td>
<td>Alive 8 years</td>
</tr>
</tbody>
</table>

TABLE 2. Five-year survivals
the former and 8 years in the latter.

**Discussion**

Reviewing the literature concerned with radiation therapy of colorectal carcinoma has shown a few 5-year survivals (Williams and Horwitz 1956; Wang and Schulz 1962; Urdaneta-Lafee et al. 1972). However, it has been generally understood that radiotherapy has no place as a curative procedure, but it is useful to get good palliation for advanced carcinoma of the rectum. Also, it is issued that radiation therapy may be effective as an adjuvant therapy of surgical treatment for advanced rectal carcinoma (Higgins et al. 1975; Ghossein et al. 1979).

The results of recent studies (Papillon 1975; Syed et al. 1978; Wassif 1983) and our present study in radiotherapy of rectal carcinoma may present encouraging data to the management of this malignancy. If all malignant lesions of primary tumor and regional lymph node metastases are perfectly included in the irradiation fields and relatively radioresistant adenocarcinoma of the rectum is eradicated by radiation, curative possibility of rectal carcinoma will be expected by radiotherapy.

Intracavitary irradiation for small and limited carcinoma in the lower rectum, which was thought to have no lymph node metastasis, revealed excellent results with high control rate of primary tumor and 5-year survival rate of 78% (Papillon 1975). A combination of external irradiation and interstitial implantation of Ir-192 for relatively extensive carcinoma of the lower rectum showed good response of primary tumor (Syed et al. 1978). In these 2 modalities, the treatment volume is restricted to primary tumor and the delivered tumor dose is 100 Gy or more. To treat advanced carcinoma of the rectum, large treatment volume must be prepared, including primary tumor and regional lymph node. The whole pelvis is chosen as irradiation field in this study. Furthermore, an additional field for paraaortic lymph node plus the whole pelvis is planned in the other report (Wassif 1983). The delivered tumor dose to such enlarged volume must be reduced to avoid radiation injury of the neighboring organs. The tumor dose, thought to be rational, will be 60 Gy in the whole pelvis irradiation and 40 Gy in the irradiation of the paraaortic lymph node. In these circumstances, supplemental irradiation with the dose of about 10 Gy is recommended to the limited volume of primary tumor.

By our analysis, it is suggested that radiation response of adenocarcinoma in the rectum is probably higher, as compared with that of adenocarcinoma in the stomach (Asakawa et al. 1982). However, local control rate in advanced carcinoma of the rectum will not exceed the level of 30% by external irradiation of 60–70 Gy, even if the combined anti-cancer drugs will increase radiation effect. In addition, it is indicated that the anti-cancer drugs will not be able to control perfectly the distant metastasis of this malignancy. So, in this combination
therapy, the curative possibility is only expected to the patients with radio-responsive tumor, whose tumor has not extended beyond the pelvis, and five-year survival rate in advanced rectal cancer will be estimated to be about 20%.

On the other hand, the relief of subjective symptoms, such as pain and bleeding, is observed in 50% or more of the patients with advanced and recurrent carcinoma of the rectum by radiation therapy. Because it is difficult to obtain such palliation by other modalities, the role of radiation therapy for the patients who are considered to have no chance of cure by any treatment will be significant and in palliative radiotherapy the dose of 40-50 Gy will be optimal.

Finally, it was reported that postoperative radiotherapy for the patients at a high risk of failure resulted in a low incidence of local recurrence (Ghossein et al. 1979). In this study, a definitive residual lesion was controlled in two of 13 patients by postoperative irradiation. So, it is suggested that postoperative radiotherapy may be valuable to control the suspicious or definite residual lesion, if the residum is restricted to the pelvis.

References