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Abstract

Between November 1984 and August 1992 we used hyperthermotherapy in six cases of local recurrence of rectal cancer. Hyperthermotherapy was performed on the average 8.7 times (range: 3-18) for each patient for 60 min each. All patients underwent combined radiotherapy and received a mean radiation dose of 42.5 Gy (range: 9-60 Gy). Five patients underwent heating within 1 h after irradiation and one patient simultaneously with the irradiation. Four patients underwent combined chemotherapy and two patients immunotherapy. Before the treatment all patients had painful lesions, but pain decreased posttherapeutically in five patients. Performance status improved in two patients. High carcinoembryonic antigen levels prior to the therapy in four patients decreased in all cases after treatment. Posttherapeutical computed tomograms revealed only minor response or no changes. After the treatment, four patients died of exacerbations of recurrent tumors and one patient of distant metastases. The patient who underwent simultaneous radiohyperthermotherapy is presently alive, in August 1992, 38 months after initiation of the treatment. The 50% survival time after initiation of the treatment was 25 months (range: 10-38 months). Hyperthermotherapy combined with radiotherapy, chemotherapy and/or immunotherapy was useful for the alleviation of pain in patients who developed local recurrence after surgery, and improved survival after recurrences can be expected.

KEYWORDS: rectal cancer, local recurrence, hyperthermia, radiotherapy, chemotherapy

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Hyperthermotherapy for Postoperative Local Recurrences of Rectal Cancer

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Between November 1984 and August 1992 we used hyperthermotherapy in six cases of local recurrence of rectal cancer. Hyperthermotherapy was performed on the average 8.7 times (range: 3-18) for each patient for 60 min each. All patients underwent combined radiotherapy and received a mean radiation dose of 42.5 Gy (range: 9-60 Gy). Five patients underwent heating within 1 h after irradiation and one patient simultaneously with the irradiation. Four patients underwent combined chemotherapy and two patients immunotherapy. Before the treatment all patients had painful lesions, but pain decreased posttherapeutically in five patients. Performance status improved in two patients. High carcinoembryonic antigen levels prior to the therapy in four patients decreased in all cases after treatment. Posttherapeutical computed tomograms revealed only minor response or no changes. After the treatment, four patients died of exacerbations of recurrent tumors and one patient of distant metastases. The patient who underwent simultaneous radiohyperthermotherapy is presently alive, in August 1992, 38 months after initiation of the treatment. The 50% survival time after initiation of the treatment was 25 months (range: 10-38 months). Hyperthermotherapy combined with radiotherapy, chemotherapy and/or immunotherapy was useful for the alleviation of pain in patients who developed local recurrence after surgery, and improved survival after recurrences can be expected.

Key words : **rectal cancer, local recurrence, hyperthermia, radiotherapy, chemotherapy**

The most frequent forms of postoperative recurrences of rectal cancer are local recurrences (1, 2) which are often unresectable and thus treated with chemotherapy or radiotherapy. Median survival time after chemotherapy or radiotherapy is approximately one year (1, 2). Few reports deal with clinical application of hyperthermotherapy in cases of local recurrences. In particular, there are only few reports on prognosis after hyperthermotherapy. We used hyperthermotherapy for postoperative recurrences of rectal cancer within a framework of a multidisciplinary therapy and achieved improvement in prognosis.

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Subjects and Methods

Subjects of the present study were six patients whose local recurrences were diagnosed at an average of 19 months (range: 7-48 months) after surgery for rectal cancer (Table 1). These patients included three men and three women and had an average age of 50 years (range: 39-67 years). The patients were treated at the Okayama University Medical School Hospital between November 1984 and August 1992. Histological types found during surgery for rectal cancer included well and poorly differentiated adenocarcinomas in one case each, moderately differentiated adenocarcinoma and mucinous car-

Table 1 Clinical charactaristics of patients

Cases	Age (yr) & Sex	Histology	Location[a] & pathological stage[b]	Conditions of recurrence		
				Maximum tumor size (cm)	Subjective symptoms	Associated symptoms
1	44F	Well diff. adenocarcinoma	Ra $SiN_2P_2H_0$	4.7	Perineal pain	Peritoneal disseminated metastasis Bladder invasion
2	39M	Poorly diff. adenocarcinoma	Rb $A_1N_0P_0H_0$	10.3	Low back pain Rt. femoral pain	Bladder invasion Rt. hydronephrosis
3	45M	Mucinous carcinoma	Rb $A_1N_1P_0H_0$	10.8	Perineal pain Low back pain	—
4	50F	Mucinous carcinoma	Rb P $A_2N_2P_0H_0$	9.0	Perineal pain	Rt. ureter invasion Rt. hydronephrosis
5	67M	Moderately diff. adenocarcinoma	Rb $A_2N_1P_0H_0$	4.0	Low back pain	Bladder invasion Lt. hydronephrosis
6	57F	Moderately diff. adenocarcinoma	Rb P $PMN_1P_0H_0$	3.6	Perineal pain Low back pain	Lung metastasis Vaginal invasion

a: Location of primary rectal cancer; Ra, upper part of rectum; Rb, inferior part of rectum; P, anal canal

b: Refer General rules for clinical and pathological studies on cancer of colon, rectum and anus, Japanese Research Society for Cancer of Colon and Rectum eds, Kanehara & Co., Ltd., Tokyo (1985) pp5–27; Si, those with invasion to other neighbor organs; A_1 those across muscle plate; A_2, those across muscle plate further, but without invasion to other neighbor organs; PM, those limited to muscle plate; No, those without nodes metastasis; N_1, those with the first group nodes metastasis; N_2, those with the second group nodes metastasis; P_0, those without peritoneal disseminated metastasis; P_2, those with a few peritoneal disseminated metastasis; H_0, those without liver metastasis

Abbreviations: yr, year; F, female; M, male; diff., differentiated; rt, right; lt, left

Table 2 Treatment methods

Cases	Hyperthermotherapy			Combined therapy		
	Heating device	Number of heating	Total heating time over 42°C (min)	Radiotherapy	Chemotherapy	Immunotherapy
1	BSD-1000 APAS	18	38	10 MV X-ray 50 Gy TDF 74.8	UFT p.o. 36000 mg	—
2	BSD-1000 APAS	8	1	10 MV X-ray 50 Gy TDF 78.2	—	nTNF-α/nIFN-α i.v. 5480×10^4U
3	BSD-1000 APAS	4	28	10 MV X-ray 9 Gy TDF 18.8	5-FU i.a. 11000 mg	nTNF-α/nIFN-α i.a. 7950×10^4U
4	BSD-1000 APAS	3	58	10 MV X-ray 36 Gy TDF 58.0	—	—
5	BSD-1000 APAS	7	7	10 MV X-ray 50 Gy TDF 80.6	Futraful i.v. 2800mg	—
6	HEH-500C	12	110	10 MV X-ray 60 Gy TDF 96.7	UFT p.o. 12600 mg	—

Abbreviations: APAS, annular phased array system; MV, million volt; Gy, gray; TDF, time, dose and fractionation; UFT, uracil plus tegaful in a molar ratio 4 : 1; 5-FU, 5-fluorouracil; p.o., per os; i.v., intravenous infusion; i.a., intraarterial infusion; nTNF-α/nIFN-α, natural human tumor necrosis factor-α and natural human interferon-α; U, unit

cinoma in two cases each. Maximum tumor diameter of the local recurrences was an average of 7.1 cm (range: 3.6 –10.8 cm). All patients complained of perineal or lumbar pain.

Table 2 shows the method of treatment. The annular phased array system of the BSD-1000 (BSD Medical Co.,

Utah, USA) was used with a frequency of 75 MHz for the hyperthermotherapy for five patients. For one patient the HEH-500C (Omron Co., Kyoto, Japan) was used at a frequency of 13.56 MHz with electrodes of 20 cm diameter, and water boluses. Each heating session lasted 60 min and sessions were held once or twice a week for an average of 8.7 times (range: 3–18 times). We measured temperature in the vesical region and tried to keep it above 42°C. All the patients underwent combined radiotherapy with 10 million volt X-rays of the LMR-15A (Toshiba Co., Kawasaki, Japan). Irradiation was given in fractions of 1.5 or 2 Gray (Gy) per session with 4 or 5 sessions per week and amounted to a total radiation of 50–60 Gy. However, irradiation was interrupted at 9 or 36 Gy in two patients, respectively, due to burns during the heating. Five patients underwent heating within 1 h after irradiation and one patient was heated simultaneously with the irradiation (3). Four out of the 6 patients received combined chemotherapy with 5-fluorouracil (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan), Futraful (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) and UFT (uracil plus tegaful in a molar ratio 4:1, Taiho). Natural human tumor necrosis factor-α and natural human interferon-α (Hayashibara Biochemical Laboratories, Inc., Okayama, Japan) were administered to two patients.

Results

During each heating session, transient pain developed depending on output from abdominal wall to perineal region with the use of BSD-1000 and directly below the electrodes with HEH-500C, and restricted the heating. The period in which the temperature of the vesical region could be maintained above 42°C, was limited to an average of 40.3 min (range: 1–110 min) and varied widely among individual patients. Two of the five patients treated with the BSD-1000 sustained cutaneous burns.

Table 3 shows the therapeutic results. Pain score of the Radiation Therapy and Oncology Study Group (4) decreased in five patients after treatment. One patient whose pain did not subside, sustained a perineal burn and received only 9 Gy of irradiation. Performance status (PS) improved in two patients. Computed tomograms (CT) taken within 1 month after the treatment showed a minor response in one case and no change in 5 cases. In case No. 6, we observed prior to the therapy a solid tumor of soft tissue density, but 1 month after the treatment the interior of the tumor had turned into a low density area (Fig. 1). In cases No. 3 and 4, the pretherapeutic CT showed extensive intratumoral low density areas and circumferential tumor parenchyma of soft tissue density. In case No. 4, thickness of the parenchyma thinned after treatment (Fig. 2). The value of the tumor marker carcinoembryonic antigen (CEA) was increased in four patients before treatment, but decreased or normalized in all patients after treatment (Fig. 3).

During the posttherapeutical follw-up, 4 patients died of exacerbations of recurrent tumors and 1 death was due to distant metastases. One patient (case No. 6) who

Table 3 Results of treatmeuts

Cases	Therapeutic effect				Side effect	Survival after treatments (month)[b]	Cause of death
	Size on CT (Reduction rate %)	Development of LDA on CT after therapy	Change of pain score[a]	Change of PS			
1	MR (25 %)	−	6→0	2→1	−	31	Peritonitis carcinomatosa
2	NC (6 %)	−	9→6	3→3	−	19	Lung metastasis Ileus due to invasion DIC
3	NC (8 %)	+	4→4	1→1	Burn on skin	10	Peritonitis carcinomatosa
4	NC (9 %)	+	9→0	2→1	Burn on skin	24	Liver metastasis Lung metastasis
5	NC (13 %)	−	4→0	1→1	−	26	Peritonitis carcinomatosa
6	NC (18 %)	+	9→2	1→1	−	38 +	—

a: Refer Tong D. *et. al.* Cancer (1982) 50, p 894.

b: Course after the start of any treatments for local recurrences until August 1992. +; alive

Abbreviations: CT, computed tomogram; MR, minor response; NC, no change; LDA, low density area; PS, performance status; DIC, disseminated intravascular coagulation

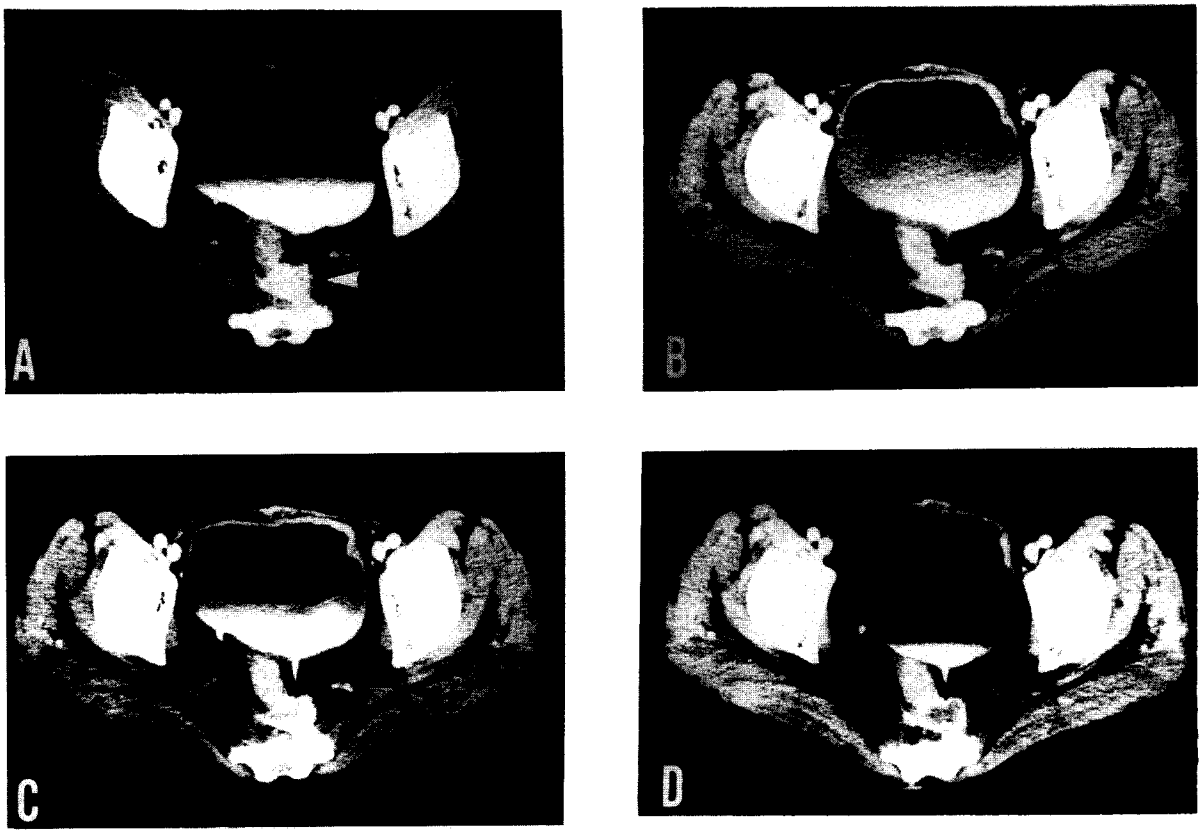

Fig. 1 CT of case No. 6. A; Before treatment. Arrow head indicates the recurrent tumor. B; Immediately after treatment. C; 1 month after treatment. D; 3 months after treatment.

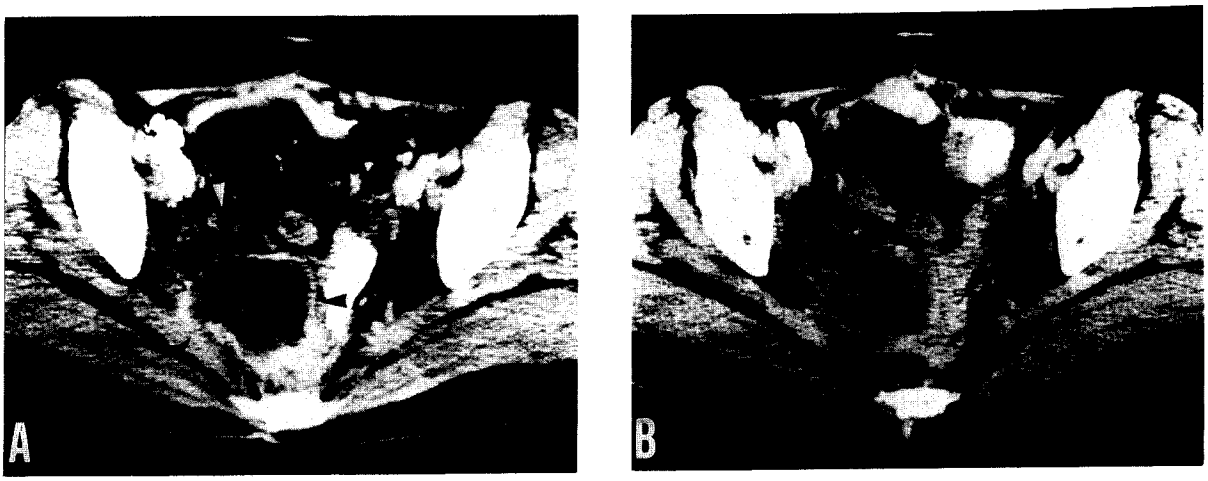

Fig. 2 CT of case No. 4. A; Before treatment. Arrow heads indicate extensive low density areas within the tumor and a thin circumferential layer of tumor parenchyma of soft tissue density. B; After treatment. Tumor parenchyma has thinned.

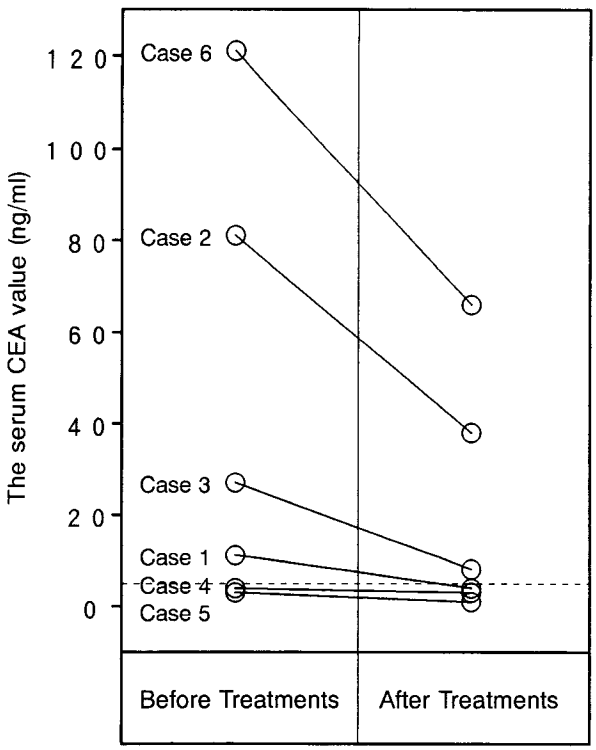

Fig. 3 Changes in serum carcinoembryonic antigen (CEA) before and after therapy. After the treatment CEA values decreased and normalized. The dotted line indicates normal upper limit (5 ng/ml).

received simultaneous radiohyperthermotherapy (SRH), is presently alive (August 1992), 38 months after initiation of the treatment of the recurrence. The 50 % survival time after the start of the treatment of the recurrence was 25 months (range: 10–38 months).

Discussion

In the treatment of rectal cancer, examination of tumor shrinkage ratio (5–7), histopathology (8) and 5-year survival rate (5, 9) revealed that hyperthermotherapy enhances the effect of irradiation. The effectiveness of hyperthermotherapy given before (5–7, 10–12) or during (13, 14) surgery and for advanced, inoperable rectal cancer (10, 12, 15), was confirmed.

The most frequent forms of postoperative recurrence of rectal cancer are local recurrences and their incidence veries between 15 and 30 % (1). However few reports deal with hyperthermotherapy for local recurrences (12, 16–21). Other therapy combined with hyperthermotherapy is reportedly useful for alleviation of pain (17, 19–21), reduction of tumor size (12, 16–18) and improvement of PS and CEA (19). In our patients it also alleviated pain and improved CEA. The extensive intratumoral low density areas on CT, which could indicate a massive coagulation necrosis (22), were observed in 3 cases. The estimation by the tumor reduction might be difficult after hyperthermotherapy if these necrosis obstruct shrinkage of the tumor (23).

Within the scope of the author's survey only a few reports deal with the prognosis of local recurrences after treatment with hyperthermotherapy. Formerly the 50 % survival time in cases of local recurrences was as short as 10 (2) or 12 (1) months. For patients with irresectable local recurrent lesions, the 50 % survival time was approximately 3 months. Even in the chemotherapy group it did not exceed 6 months, in the radiotherapy group 5 months and in the combined radio- and chemotherapy group 9 months (2). The small number of patients allows tentative conclusions from this retrospective study, but survival time after the start of the treatment of recurrences was markedly longer than after common radiochemotherapy (1, 2). However, four patients died of exacerbating recurrent lesions. More powerful local treatment forms are needed to achieve longer survival. One patient who received SRH is still alive 38 months after initiation of the treatment. According to basic *in vitro* and *in vivo* studies (24, 25), the heating enhances the effect of irradiation best during simultaneous irradiation and heating. To prevent a decrease in therapeutic gain factor (24, 25), the directions of the capacitive heating and external irradiation are adjusted to cross within the body (3). This method is safe for clinical application (26). In the future we wish to continue our investigations of SRH application within a multidisciplinary therapy.

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