# [原著] Clinical Study of Rectal Administration of FT 207 in Patients with Advanced Gastromtestinal Cancer

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# Clinical Study of Rectal Administration of FT 207 in Patients with Advanced Gastrointestinal Cancer

Akira Hokama, Yoshiyuki Sho, Yoshihiro Muto,
Kazuo Yamauchi, Kotaro Kurihara, Masahito Yamazato,
Osamu Hidaka and Kazuhiro Kaida

The First Department of Surgery, School of Medicine, University of the Ryukyus

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**Abstract**

We have administered by rectumFT 207 to inoperable cases, recurrent cases or those cases who had undergone palliative operation. Twenty three cases were treated with this method: nine cases of gastric cancer, four cases of colon cancer, four cases of rectal cancer, three cases of hepatoma, a case of biliary tract cancer, a case of liver metastasis from esophageal cancer, and a case of cancer of the anus. Daily dosage was 750 mg or 1500 mg, and the total dose ranged from 15.5g to 574.5g. Other drugs (Neocarcinostatin or Mitomycin C and Picibanil or Kresin) were also administered. According to Karnofsky's criteria, the results were as follows:six cases of O-O, a case of O-A, none of O-B, a case of O-C, seven of 1-A, four cases of 1-B, two cases of 1-C and two of unknown classification. A total of thirteen of the twenty one cases showed more than 1-A.

## Introduction

N-(2-tetrahydrofuryl) -5-fluorouracil (FT207) derived first by Gillar in 1966 is a form of a masked compound of fluorouracil ( 5 FU). It is an antimetabolic agent that impairs DNA synthesis. Its action is cytostatic and time dependent. Kimura[2] developed oral administration of FT 207 in 1972. Konda et al[3] introduced rectal administration of FT 207 in 1975.

Absorption of FT 207 from rectal mucosa is rapid and a high concentration in the blood is obtained and maintained.[4] We have undertaken rectal administration of FT 207 in twenty three patients suffering from advanced gastrointestinal cancer. The results were encouraging.

## Materials and Methods

Twenty three patients with gastrointestinal cancer who were admitted to our clinic were treated with FT 207 suppositories. The malignancies were inoperable, recurrent, or amenable only to palliative operation-i.e., nine cases of gastric cancer, four cases of colon cancer, four cases of rectal cancer, a case of liver metastasis from esophageal cancar and a case of cancer of the anus.

Daily dosage was 750 mg, 1000mg, or 1500mg. Suppositories of 750 mg or 1000 mg were given once daily or suppositories of 750 mg were used twice daily. In most of the cases,other drugs were used concomitantly: Neocarcinostatin or Mitomycin C and Picibanil or Krestin. Daily dosage of Neocarcinostatin was 2000 units for 20 days. 4 mg of Mitomycin C was used twice a week. 5 KE of Picibanil ( OK 432 ) was used once a week. Krestin was given 3 g daily. The total dose of FT 207 ranged from 15. 5 g to 574.5 g ( Table 1 ).

Table 1. Cancer Patients Treated with FT 207 Suppository

| No. | case | age sex | clinical diagnosis | dose per day (g) | days used | total dose(g) | combined drugs | outcome | effect (Karnofsky) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M.K. | 48 F | gastric carcinoma | 0.75×2 | 202 | 303 | OK432 | death 9 mo. | 1 – A |
| 2 | S.K. | 50 F | rectal ca. polyposis | 0.75×2 | 167 | 250.5 | 5 FU OK432 | death 10 mo. | 1 – A |
| 3 | H.I. | 66 M | gastric carcinoma | 0.75×2 | 29 | 43.5 | NCS OK432 | death 8 mo. | 1 – A |
| 4 | C.N. | 78 F | gastric carcinoma | 0.75×2 | 558 | 574.5 | NCS PSK | alive | 1 – C |
| 5 | M.S. | 63 M | biliary ca. rib meta. | 0.75×2 | 423 | 527.5 | OK432 PSK | death ly 9 mo. | 1 – C |
| 6 | A.S. | 55 M | colon ca. liver meta. | 0.75×1 | 77 | 115 | OK432 | death ly 4 mo. | 1 – B |
| 7 | S.S. | 52 M | hepatoma | 0.75×2 | 35 | 52 | MMC OK432 | death 10 mo. | 1 – A |
| 8 | K.S. | 78 F | anal carcinoma | 1.00×1 | 63 | 63 | cryo PSK | alive | 1 – B |
| 9 | Y.F. | 66 M | colon ca. liver meta. | 0.75×2 | 42 | 63 | SSM | death 5 mo. | 1 – A |
| 10 | H.M. | 41 F | gastric carcinoma | 0.75×1 | 98 | 73.5 | NCS PSK | death 3 mo. | 1 – A |
| 11 | T.K. | 59 F | gastric carcinoma | 0.75×1 | 56 | 42 | MFC PSK | death 2 mo. | 0 – O |
| 12 | S.U. | 78 M | rectal carcinoma | 0.75×1 1.00×1 | 259 | 257.5 | | alive | 1 – B |
| 13 | K.E. | 70 M | esophageal ca. liver metastasis | 1.00×1 | 63 | 63 | $^{60}$CO | alive | 0 – C |
| 14 | O.T. | 40 F | hepatoma | 0.75×1 | 21 | 15.5 | NCS OK432 | death 2 mo. | 0 – O |
| 15 | N.B. | 42 M | rectal carcinoma | 0.75×2 | 150 | 225 | OK432 | alive | 1 – A |
| 16 | T.H. | 62 M | rectal carcinoma | 0.75×1 0.75×2 | 35 | 51.5 | MFC | alive | 1 – A |
| 17 | A.K. | 65 M | gastric carcinoma | 0.75×2 | 14 | 24 | NCS OK432 | death 2 mo. | 0 – O |
| 18 | T.S. | 49 F | gastric carcinoma | 0.75×2 | 28 | 21 | NCS OK432 | death 2 mo. | 0 – O |
| 19 | U.Y. | 42 M | gastric carcinoma | 0.75×2 | 28 | 21 | NCS | death 2 mo. | 0 – O |
| 20 | T.S. | 47 F | gastric carcinoma | 0.75×1 | diarrhea | | NCS OK432 | death 2 mo. | 0 – O |
| 21 | T.R. | 76 M | colon ca. liver meta. | 0.75×2 0.75×1 | 59 | 51.5 | | death 2 mo. | 0 – A |
| 22 | U.T. | 49 F | colon ca. liver meta. | 0.75 ×1 | 56 | 42 | | | |
| 23 | A.M. | 28 M | hepatoma | 0.75 ×2 | 49 | 73.5 | MMC OK432 | | |

OK432: Picibanil, PSK : Krestin, NCS : Neocarcinostatin, MMC : Mitomycin C
MFC: Mitomycin C + Futraful + Cytosine Arabinoside
meta. : metastasis, mo. : month

## Results

According to Karnofsky's criteria, the results were as follows: six cases of O-O, a case of O-A, none of O-B, a case of O-C, seven cases of 1-A, four cases of 1-B, two cases of 1-C and two unknown. Sixty two per cent ( thirteen of the twenty one cases ) showed more than 1-A. Side effects of rectal administration of FT 207 were minimal, and only two patients discontinued usage because of diarrhea.

## Case Reports

Case 1. M.K., a 48 year old housewife was admitted on June 28, 1977 with the chief complaint of lower abdominal pain and tarry stools. On physical examination she had a palpable mass in the epigastrium and rectal examination revealed a 2.5 × 3 cm sized tumor with ulceration 3 cm above the anal ring. Upper GI series and gastrofiberscopic examination revealed a Borrmann III type of gastric cancer. Biopsy of the rectal tumor revealed adenocarcinoma (Fig. 1.)

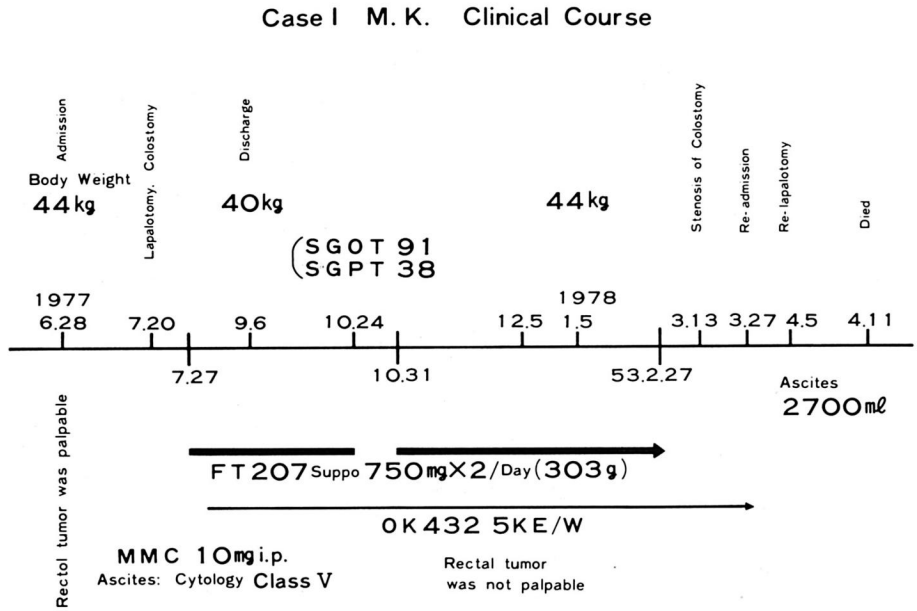


Fig. 1 Cilinical course of Case 1.

Laparotomy was carried out on July 20, 1977, and peritoneal carcinomatosis and malignant ascites were discovered. A Krukenberg's tumor of left ovary was observed. A sigmoid colostomy was created. One week after operation chemotherapy was begun with FT 207 suppositories, giving 750 mg twice daily. At the same time 5 KE of OK 432 ( Picibanil ) was used once a week. She was discharged on September 6 and the chemotherapy was continued in the outpatient clinic. Interestingly, the rectal tumor had disappeared by the beginning of December, and she had gained 4 kg of body weight since

she had been discharged. She was readmitted on March 27 in 1978 with symptoms of anorexia and abdominal pain, and gradually deteriorated and ultimately died on April 11 in 1978. The total dose of FT 207 was 303 g. Autopsy revealed peritoneal carcinomatosis, a 2 × 2 cm sized tumor of the anterior wall of the stomach, and intestinal obstruction ( ileal and colonic )due to dissemination of the tumor. Gross tumor was not seen in the rectum, but microscopic examination showed submucosal infiltration of signet cell carcinoma (Fig.2 )

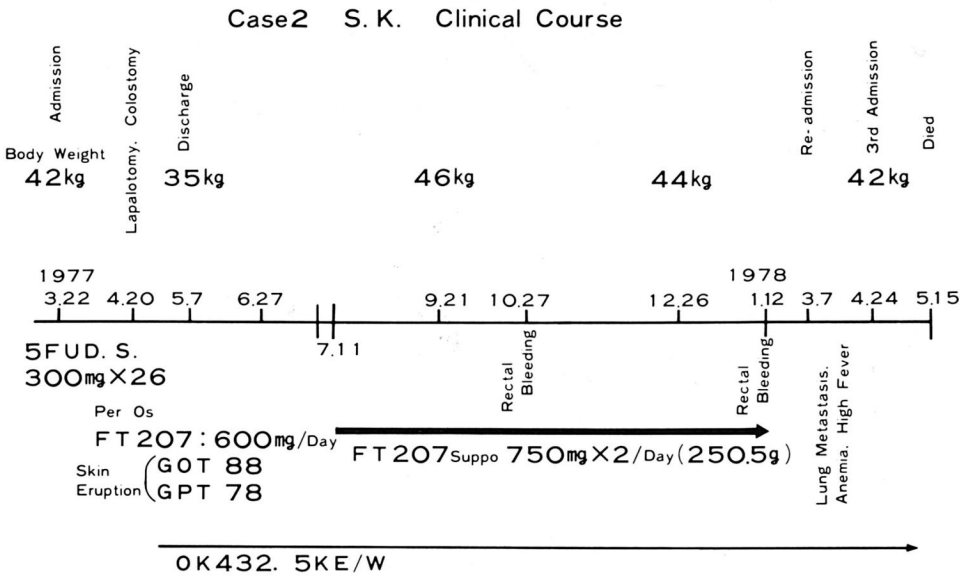


Fig. 2 Cilinical course of Case 2.

Case 2. S.K., a fifty year old housewife was referred to us with the chief complaint of bloody,mucus laden stools for a month's duration. She had lost about 10 Kg of body weight in the preceding six months. Barium enema showed multiple polyps of the entire colon. Family history revealed that a younger brother had died of gastric cancer and a younger sister had died of an abdominal malignancy at the age of 40. Familial polyposis was suspected. Digital examination of the rectum revealed a tumor at 5 cm above the anal ring. Biopsy revealed papillary adenocarcinoma. Laparotomy was carried out on April 20, 1977, but because of locally invasive tumor, curative resection could not be accomplished. A sigmoid colostomy was created. After surgery, oral administration of FT 207 was begun, but it was soon discontinued because of skin eruption and elevation of SGOT and SGPT. Rectal administration of FT 207 was started on July 11, and was continued until January 11, 1978 in the outpatient clinic when rectal bleeding ocurred again.

She was readmitted on April 24 and was found to have lung metastases and anemia. The patient died on May 15, 1978. She had gained 11 kg of her body weight during the period that she had received chemotherapy, and she was able to work for several months. The total dose of FT 207 was 250.5 g.

Case 5. M.S., a 63-year-old male was admitted on December 5, 1977 with the chief complaint of jaundice and a tumor on the left side of the chest wall. Scout x-ray of the abdomen showed a calcified density in the right upper abdomen. The tumor of the chest wall was an osteolytic lesion of the 9th rib. Scintiscanning with $^{99m}$Tc showed accumulation of the isotope at the tumor site, and it was suspected to be a metastatic lesion. Cholecystectomy and resection of the 9th rib were performed on April 19, 1978. Inflammatory change was heavy around the gallbladder and duodenum. The liver was free of any tumor. An operative cholangiogram showed stenosis of the distal portion of the common bile duct. Pathologic examination revealed cholelithiasis with acute and chronic cholecystitis, a metastatic adenocarcinoma involving the rib. After surgery repeated endoscopic examination of the duodenum revealed adenocarcinoma, but radical pancreaticoduodenectomy was not considered due to distant metastases. He was discharged on June 3, and rectal administration of FT 207 and combination of OK 432 were continued in the outpatient clinic. He was readmitted on April 12, 1979 with high fever and jaundice. PTCD was performed on April 25 and jaundice improved gradually. The distal portion of the common bile duct showed complete obstruction. On November 27, choledocho-jejunostomy was carried out, but after that he went down hill and died on March 14, 1980. Although he had distant metastatic lesions, he had lived more than two years. The total dose of FT 207 was 527.25 g.

## Discussion and Conclusion

All cases that were treated with FT 207 suppositories are listed in table 1. Most of the cases were combined with other anticancer drugs ( Neocarcinostatin or Mitomycin ). Picibanil ( OK 432 ) or Krestin ( PSK ) were also used as immunopotentiators. Case 1, Case 2 and Case 5 were presented in detail. Case 8 was a 78 year old female who had anal cancer. As the patient refused conventional operation, cryosurgery was carried out and the tumor was necrotized superficially. Thereafter suppositories of FT 207 were used for 259 days. Fifteen months later she was readmitted because of metastasis to left inguinal lymph nodes. Irradiation with Co of the lesion was done in doses totalling 5000 rads. Three years and seven months have passed since she first visited our clinic. She is still doing well without colostomy.

Among the numerous methods of administering chemotherapy for abvanced gastrointestinal cancer, rectal administration of FT 207 has several advantages. Patients can use it by themselves on the outpatient bases without difficulty. No severe side effects were observed. Only two patients stopped usage because of diarrhea. Effects on hematology data and liver function are shown in Figures 3 and 4, and no untoward tendencies were identified ( Fig. 3, 4 ). In Case 1 slight elevation of SGOT was noted, but it returned soon to normal range and administration of the suppository was continued. Figure 5 shows relation between total doses and clinical effects. Out of twenty one cases thirteen showed more than 1-A in Karnofsky's criteria, which was sixty two per cent effectiveness ( Fig.5 ). Mean total dosage of FT 207 in 22 cases was 134.2 g and mean duration of

the administration was 114 days. Preferable clinical effects were dominant in those cases which had received more than 50 g. Nakano stated that clinical effects would be expected above total dosage of 60 g. Response rate ranges from 9.8% to 68.8% according to the difference of patient materials, dosage or combined radiotherapy.

In our series, rectal administration of FT 207 has proved to be an useful method in chemotherapy for patients with advanced gastrointestinal cancer.

( The summary of this paper was presented at the 16th Congress of Japanese Society of Gastroenterological Surgery in Kyoto, 1980 ).

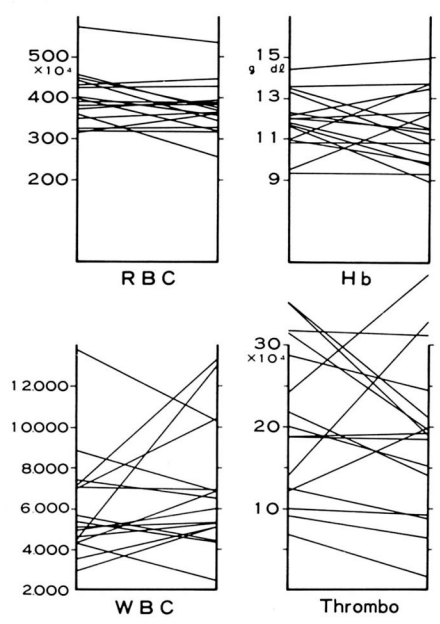


Fig. 3 Influence on hematology

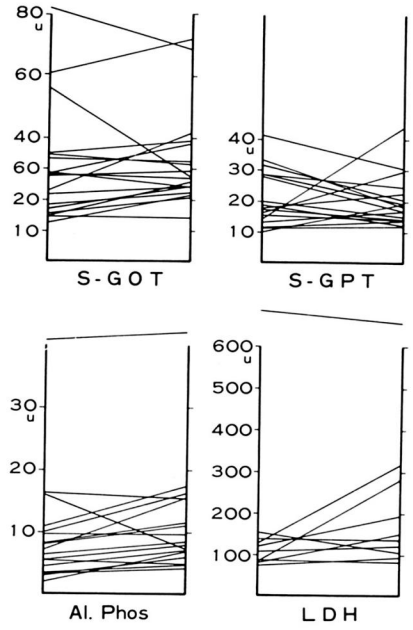


Fig. 4 Influence on serum enzymes.

| Total Dose | Number of Patients | Clinical Effects (Karnofsky) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 0-0 | 0-A | 0-B | 0-C | I-A | I-B | I-C |
| 50g | 9 | ●●● ●●● | | | | ●○ | | |
| 50g ~ | 6 | | ● | | ○ | ●●● | ○ | |
| 100g ~ | 2 | | | | | | ● | |
| 200g ~ | 3 | | | | | ●○ | ○ | |
| 300g ~ | 1 | | | | | | ● | |
| 500g ~ | 2 | | | | | | | ●○ |
| Total Cases | 23 | 6 | 1 | | 1 | 7 | 4 | 2 |

● Dead ○ Alive 2 Cases : unknown

( 1980 7 )

Fig. 5 Relationship between total dose of Futraful suppository and clinical effects.

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