

Complete Response of Highly Advanced Colon Cancer with Multiple Lymph Node Metastases to Irinotecan Combined with UFT: Report of a Case

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Abstract

Massive lymph node metastasis of the para-aortic region and supraclavicular lymph nodes, Virchow's lymph node metastasis due to colon cancer, is extremely rare. We herein report a case of such systemic lymph node metastasis that was successfully treated with a combination of irinotecan (CPT-11) and UFT, a combination drug of tegafur and uracil. The patient was a 57-year-old woman who had a tumor in the ascending colon, and massively swollen para-aortic and supraclavicular lymph node metastasis. She was treated with combination chemotherapy of CPT-11 and UFT. The main tumor was detected as a decompressed scar, and the supraclavicular and para-aortic lymph nodes had completely disappeared after the second cycle of treatment. A histopathological examination and immunohistochemistry with cytokeratin showed complete remission of adenocarcinoma in the tumor and para-aortic lymph nodes. She remains alive without recurrence 52 months after chemotherapy. Combination chemotherapy of CPT-11 and UFT may be of potential value in the treatment of advanced colorectal carcinoma, and both histopathological and immunohistochemical confirmation of a complete remission may indicate prolonged disease-free survival.

Key words Colon cancer · Advanced lymph node metastasis · CPT-11/UFT · Immunohistochemistry · Complete remission

Introduction

In colorectal cancer, 5-fluorouracil (5-FU) has been the mainstay of adjuvant treatment and treatment of metastatic disease for many years.¹ Although efforts to improve efficacy through schedule modification, including prolonged infusions, have been made, its efficacy has been limited. New agents with improved efficacy, tolerability, and ease of administration are required. Among the newer drugs, irinotecan (CPT-11) is becoming established as a first- and second-line treatment for advanced disease.^{2–4} Its novel mechanisms of action have proven to be of value in 5-FU-resistant patients.

UFT is a combination drug of the prodrug tegafur and uracil in a 1:4 molar ratio.⁵ Uracil is a reversible inhibitor of the enzyme dihydropyrimidine dehydrogenase (DPD), which is responsible for the catabolism of 5-FU. Combining these drugs would be anticipated to increase the response rates while maintaining the advantages of a regimen based on an orally administered fluoropyrimidine. Ohshiro et al. conducted a phase I study of CPT-11 and UFT in patients with advanced or metastatic gastrointestinal cancers, and demonstrated its safety and potential efficacy.⁶ The recommended dose for a phase II study was CPT-11 150 mg/m² bi-weekly, and UFT 375 mg/m² on days 3–7, 10–14, 17–21, 24–28 in 4–5 weeks. They demonstrated a response rate of 42% in the 19 evaluable patients with only grade 3 adverse events of leukopenia or neutropenia.

At that time, leucovorin had not become commercially available in Japan; therefore, we conducted a phase II study of this regimen in patients with advanced or metastatic colorectal cancer to find out its safety and efficacy. We employed oral UFT-E instead of UFT capsules. UFT-E, enteric-coated granules, was designed to reduce gastrointestinal adverse events, and has been

demonstrated to have a significantly lower incidence of nausea and vomiting, while maintaining its activity.⁷

We herein report the case of a female patient with highly advanced cancer of the right colon with multiple para-aortic and supraclavicular lymph node metastases, who was recruited to this phase II study and was successfully treated with both CPT-11/UFT and surgical intervention.

Case Report

A 57-year-old woman with a 2-month history of general fatigue, abdominal discomfort, and left neck and arm swelling was referred to Osaka University Hospital. On physical examination, multiple tumors measuring up to 5 cm in diameter were palpable in the left neck and supraclavicular region. The serum carcinoembryonic antigen (CEA) level was 23 ng/ml (normal range, <5 ng/ml). All other laboratory findings were all within normal ranges.

Colonoscopy (Fig. 1A) showed type 3 advanced cancer in the ascending colon. A biopsy specimen showed poorly differentiated adenocarcinoma (Fig. 1B). A neck computed tomography (CT) scan revealed bulky swollen lymph nodes in the supraclavicular area, resulting in a complete obstruction of the left internal jugular vein and innominate vein (arrowhead, Fig. 2A). A bypassed

flow around the tumors was detected as a subcutaneous contrast media (arrows in Fig. 2A). An abdominal CT scan also showed multiple lymph node swelling in the para-aortic region (Fig. 2B). Metastasis of poorly differentiated adenocarcinoma was diagnosed by fine-needle aspiration cytology of a cervical swollen lymph node. As the tumor was highly advanced, we planned to administer systemic chemotherapy. After discussing the various chemotherapeutic treatment options, the patient decided to participate in an ongoing phase II study of our institution, which is evaluating the toxicity and antitumor efficacy of combined chemotherapy of CPT-11 and UFT in patients with advanced colorectal cancer. She was fully eligible for this phase II study and written informed consent was obtained.

Treatment Schedules

According to the protocol, CPT-11 150mg/m² was administered over 90 min by intravenous infusion on days 1 and 15. UFT, 375 mg/m² was orally administered on days 3–7, 10–14, 17–21, and 24–28. One cycle of this treatment was 35 days. The patient was treated with an actual dose of 200mg of CPT-11 and 500mg of daily UFT. She experienced grade 3 nausea and vomiting during the first cycle of treatment, but not during the second. She was taken off the study due to grade 4 neutropenia on day 25 of the second cycle.

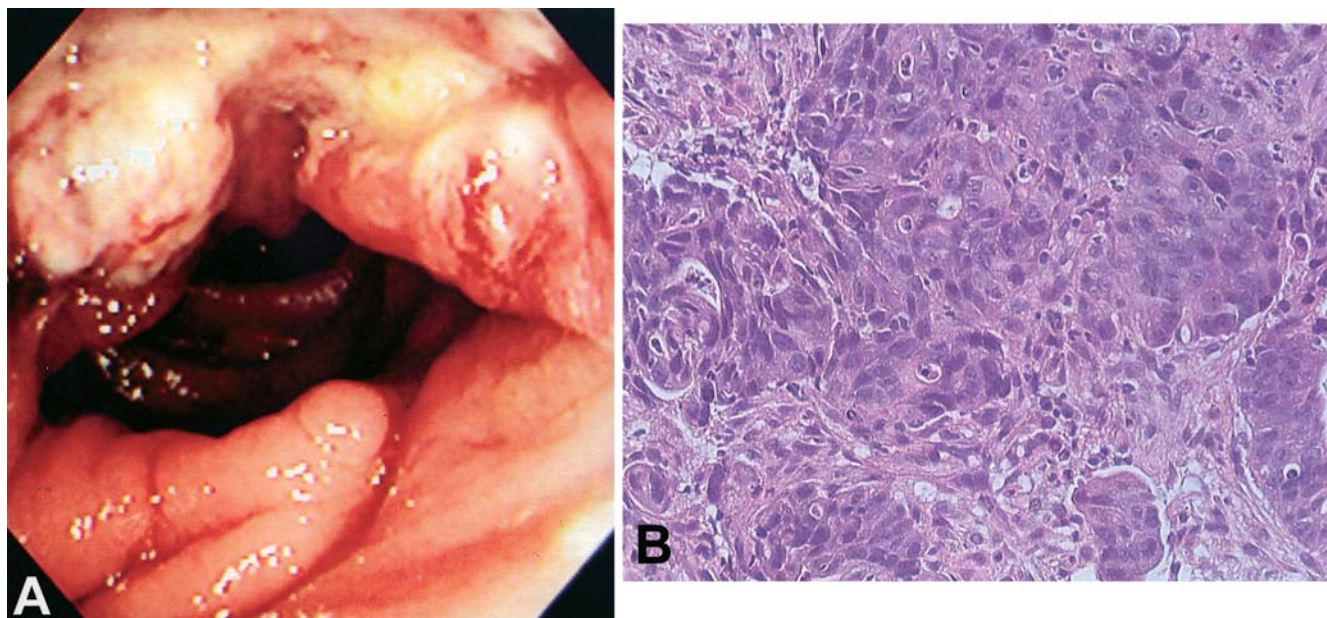


Fig. 1A,B. Colonoscopic findings at first diagnosis and a representative microscopic section of the biopsy (**B** H&E, $\times 200$). Type 3 advanced carcinoma in the right colon. Preservation of the luminal patency and no bleeding tendency were observed.

Colonic mucosa with a diffuse infiltrate of PAS-positive tumor cells and an enlarged nucleolus. Histopathological diagnosis: poorly differentiated adenocarcinoma of the right colon

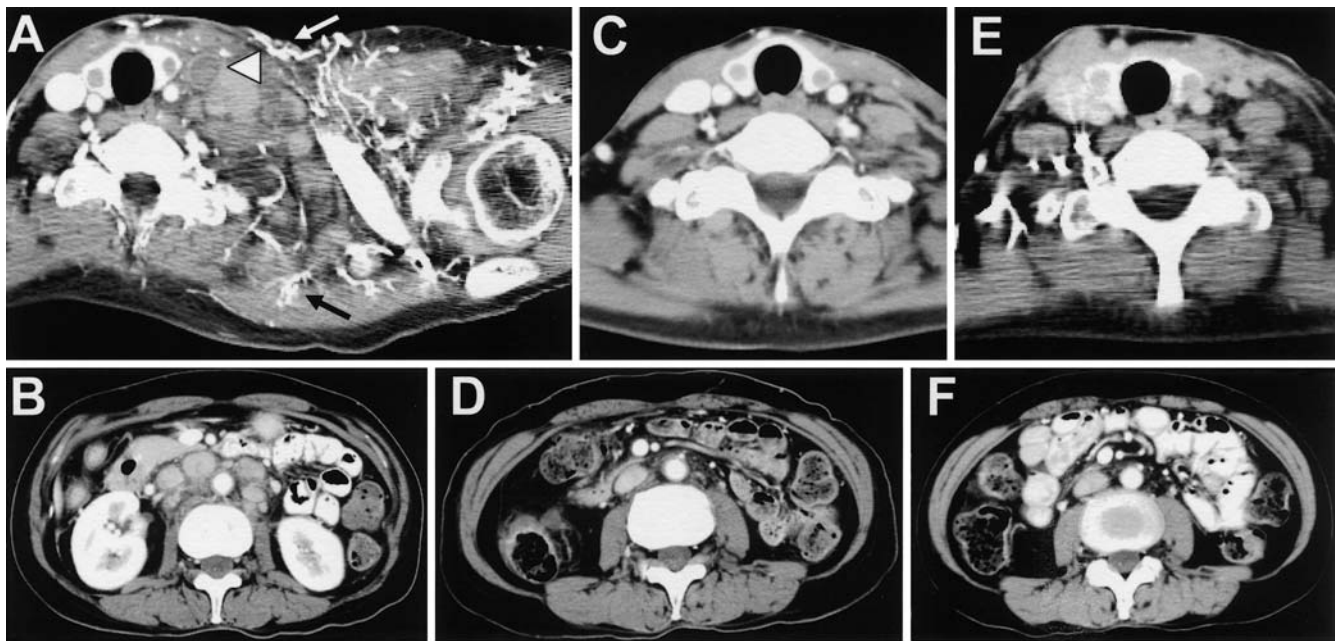


Fig. 2. Neck and abdominal computed tomography scans at first diagnosis (**A**, **B**), one cycle after chemotherapy (**C**, **D**), and two cycles after chemotherapy (**E**, **F**). **A** Bulky swollen lymph nodes in the left supraclavicular portion with a complete obstruction of the left internal jugular vein (*arrowhead*)

and a bypassed flow around the tumors (*arrows*). **B** Multiple areas of lymph node swelling were also found in the para-aortic region. **C–F** The swollen lymph nodes at both sites decreased in size after chemotherapy

Objective Response and Toxicities

The response was evaluated by CT after each cycle, and after two cycles by endoscopy according to Response Evaluation Criteria In Solid Tumors.⁸ After one treatment cycle, the supraclavicular lymph nodes had disappeared (Fig. 2C), and they still disappeared after two cycles of treatment (Fig. 2E). Para-aortic lymph nodes were also undetectable after one (Fig. 2D) and two (Fig. 2F) cycles of treatment. Figure 3A shows the endoscopic findings, i.e., that the cancer of the right colon was only a decompressed scar. Four biopsy specimens were obtained and no residual tumor was found. The serum CEA level was normalized after one cycle of treatment (3 ng/ml) and was only 1 ng/ml after the second cycle. Taken together, these parameters indicated that a complete response was obtained.

Pharmacokinetic Parameters

On day 1 of the first cycle, the fluctuation of the level of serum SN-38, an active metabolite of CPT-11, was followed before administration, and at 0, 1, 2, 8, 12, and 24 h after administration. On day 3 of the first cycle, serum levels of 5-FU before, and at 1, 2, 4, and 8 h after UFT administration were also examined. Next, the pharmacokinetic parameters, for example C_{\max} (ng/ml) and AUC (ng/h/ml), were calculated. C_{\max} and AUC_{0–25.5}

of SN-38 were 79.1 and 517, respectively. C_{\max} and AUC_{0–8} of 5-FU were 337 and 917, respectively.

Operation Findings

A resection of the right colon with an extended lymphadenectomy including of the para-aortic region was planned in order to remove the primary region and to make a pathological diagnosis. An upper abdominal incision was made to enter the abdomen. No evidence of ascites, liver metastasis, peritoneal dissemination, or regional lymph node swelling was detected. The primary tumor region was detected because of the scar-like serosal change; however, the tumor was not detected by palpation. A para-aortic lymph node dissection was performed at levels between the diaphragm and aortic bifurcation. Because tissues containing para-aortic lymph nodes strongly adhered to the aorta and inferior vena cava, a sharp dissection was performed to remove these tissues. End-to-side iliocolic anastomosis was done for reconstruction.

Pathological Findings

In the resected specimen, the primary region was detected only as a decompressed scar (Fig. 3B). A histopathological examination of the resected primary

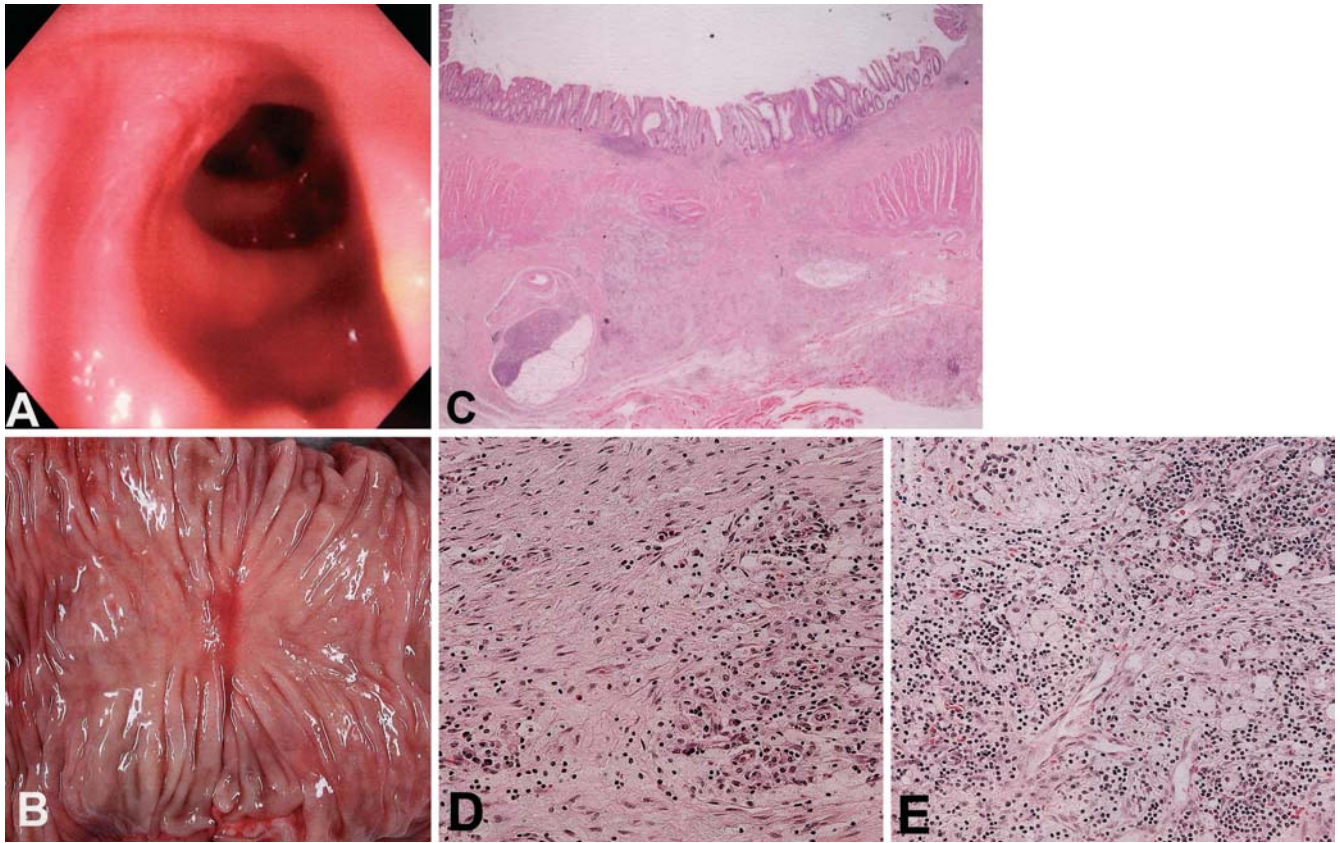


Fig. 3. **A** Colonoscopic findings two cycles after chemotherapy. **B** A macroscopic photograph of the resected specimen. The primary region was reduced to only a scar. **C–E** Representative sections of the resected specimen with H&E. **C** The whole appearance of the primary lesion ($\times 12.5$). The muscularis propria layer is torn, presumably by the cancer cell

invasion, and this area is covered by a normal mucosa. **D,E** Strong magnification ($\times 200$) of **D** the primary lesion and **E** one of the para-aortic lymph nodes. Diffuse fibrosis and aggregation of foam cells were observed. No viable cancer cells were detected

region and para-aortic lymph nodes showed no viable cancer cells (Fig. 3C–E). Four consecutive slices of 4- μ m thick sections were made from the primary tumor and all resected lymph nodes, and were subjected immunohistochemistry. Immunostaining was performed on the TechMate Horizon automated staining system (DAKO, Glostrup, Denmark), as described previously.⁹ Briefly, after blocking with bovine serum albumin, the sections were incubated with pancytokeratin monoclonal antibody AE1/AE3 (DAKO, Carpinteria, CA, USA), which has been previously used for the detection of micrometastases.^{10,11} This monoclonal antibody has the broadest spectrum of keratin reactivity among human epidermal keratins, and it produces positive staining in virtually all cancer cells arising from the human epithelium. They were then incubated with antimouse secondary antibody conjugated with dextran polylinker (EnVision plus; DAKO). A histological examination of biopsy specimen before chemotherapy showed positive staining with the cytokeratin antibody. However, posi-

tively stained cells were detected neither in a biopsy specimen before operation nor in the resected tumor by immunohistochemistry with cytokeratin antibody, and a histological complete remission was thus confirmed.

Postoperative Course

Because of ptosis of the stomach and paralysis of the duodenum, oral intake was insufficient for 1 month. However, it recovered thereafter and postoperative chemotherapy using CPT-11 and UFT was started 10 weeks after operation with dose modification. The patient received 150 mg/body CPT-11 and 300 mg/body/day UFT. After two cycles of treatment, she had a bowel obstruction, which required surgical intervention. After surgery she was followed up without any chemotherapy. The serum CEA level remained within the normal range and no tumor recurrence has been detected on either abdominal or neck CT. She remains alive without recurrence at 49 months after surgery.

Discussion

In colorectal carcinoma, up to 20% of all patients present with stage IV disease at initial diagnosis.^{12–14} Liver, lung, and peritoneum are the most frequently observed metastatic sites. In 89 patients in the series of Scoggins et al., sites of metastasis were liver 85% (76/89), lung only 4% (4/89), and peritoneum 10% (9/89).¹³ In other series of a total of 144 stage IV colorectal cancers, no case with massive lymph node metastasis was documented.^{14,15} Case reports of colorectal cancer with massive lymph node metastasis including supraclavicular lymph nodes at first diagnosis are found in Japan, but the true incidence of such cases is unclear.^{16–19} The prognosis of patients with stage IV colorectal carcinoma remains poor, with the median survival just 9–10.3 months,^{14,20–22} and decision-making in such advanced cases is extremely difficult. Cases in which there is bowel obstruction or bleeding due to tumor progression may need a resection of the primary region.^{11,12} A resection of primary and liver metastasis is recommended as long as hepatic metastasis occupies less than 50% of liver volume, although postoperative mortality and morbidity are relatively high.^{13,18,20} However, decision-making in the treatment of systemic lymph node metastasis has not been fully described. Adjuvant chemotherapy following a resection of the primary tumor was performed in all case reports in Japan,^{16–19} because of either bowel obstruction or no available effective regimen for neoadjuvant chemotherapy. As the prognosis of these patients was poor, another treatment strategy is necessary for patients without bowel obstruction, which requires surgical intervention. With the advent of active agents such as irinotecan and oxaliplatin,^{2,3,16,23} we can anticipate different strategies for those intractable cases, i.e., down-staging by chemotherapy followed by surgical intervention. The achievement of down-staging may not only reduce operative complications but also increase the number of curatively resected cases. Because the patency of the right colon was well preserved and severe bleeding tendency was not observed under observation by colonoscopy, we thus planned to start chemotherapy on this patient.

The treatment regimen includes CPT-11 (150 mg/m²), given as a 90-min intravenous infusion on days 1 and 15, followed by twice-daily UFT (500 mg) on days 3–7, 10–14, 17–21, and 24–28. The cycles are repeated every 35 days for two cycles. In this patient, grade 3 nonhematological toxicity (appetite loss) was noted in the first cycle and grade 4 neutropenia in the second cycle, which resulted in the cessation of UFT on day 24. C_{\max} and AUC of SN-38 (CPT-11, 150 mg/m² administration) were previously reported as 31–42 (ng/ml) and 197–354 (ng/h/ml), respectively.^{24,25} In comparison to these data, the C_{\max} (79.1) and AUC (517) of SN-38 in

our patient were very high. The C_{\max} (337) and AUC_{0–8h} (917) of 5-FU after oral administration of UFT were also high in comparison to the findings of previous study (C_{\max} : 245 ng/ml and AUC_{0–8h}: 223 ng/h/ml).⁵ These results suggest that our patient was exposed to a sufficient chemotherapeutic agent, which led to a complete remission and grade 4 hematological toxicity. This patient had a bowel obstruction after two courses of postoperative chemotherapy. We still do not know the direct relationship between CPT-11 and bowel obstruction; however, CPT-11-induced colitis has been reported, which may enhance postoperative bowel adhesion.²⁶ We thus need to pay attention to this complication.

Continuing chemotherapy without surgical intervention might be another treatment option. Because only 2%–3% of patients have a complete response,²⁷ and tumor relapse after complete remission is frequently observed,²⁸ we carried out surgery for the purpose of histological diagnosis and cure. The confirmation of a histological complete remission with hematoxylin and eosin staining and immunohistochemistry meant that we abandoned the planned mediastinal and neck lymph node dissection. A further follow-up is definitely needed in this patient, because patients with a complete response have a long median overall survival, which is as long as 30 months.²⁷

In summary, we herein reported a case of highly advanced massive lymph node metastasis from cancer of the right colon, which was successfully treated with combination chemotherapy and surgical intervention. Although a careful follow-up of this patient is obligatory, a complete pathological response was demonstrated. Combination chemotherapy of CPT-11 and UFT is thus considered to be of potential value in the treatment for advanced colorectal carcinoma.

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