研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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IV. 研究成果の刊行物・別刷

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CLINICAL INVESTIGATION

Hepatic Arterial Infusion Chemotherapy through a Port-Catheter System as Preoperative Initial Therapy in Patients with Advanced Liver Dysfunction due to Synchronous and Unresectable Liver Metastases from Colorectal Cancer

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Abstract

Purpose We retrospectively evaluated the safety and efficacy of preoperative initial hepatic arterial infusion chemotherapy (HAIC) through a port-catheter system in patients with liver dysfunction due to synchronous and unresectable liver metastases. The aim of HAIC was to improve patients' clinical condition for later surgical removal of primary colorectal cancer.

Methods Port-catheter systems were placed radiologically in 21 patients (mean age 58.6 ± 8.1 years) with liver dysfunction due to synchronous liver metastases from colorectal cancer. Initial HAIC of 1,000 mg/m^2 5-fluorouracil was administered weekly as a 5 hr continuous infusion through this system. Surgical removal of the primary lesion was planned after HAIC improved the liver function.

Results Port-catheter system placement was successful in all patients without severe complications. Patients were followed up for a median of 309 days (range 51–998 days). After starting HAIC, no severe adverse events that caused drug loss and treatment postponement or suspension were observed in any of the patients. HAIC was performed a mean of 4.5 ± 3.0 times and the liver function improved in all patients. Curative (n = 18) or palliative (n = 1) surgical removal of the primary lesion was performed. The remaining 2 patients died because extrahepatic metastases developed and their performance status worsened; thus, surgery could not be performed. The median survival times of all patients and the operated patients were 309 and 386 days, respectively.

Conclusion Initial HAIC administration is a safe and efficacious method for improving liver function prior to operative resection of primary colorectal cancer in patients with liver dysfunction due to synchronous and unresectable liver metastases.

Keywords Colorectal cancer · Hepatic arterial infusion chemotherapy · Liver metastasis · Port-catheter system

Introduction

Colorectal cancer is the fourth most commonly diagnosed malignant disease worldwide [1], and synchronous liver metastases are identified in 10–20% of cases [2]. However, the treatment protocol for patients with stage IV colorectal cancer with synchronous liver metastases has not been firmly established [2, 3]. In such patients, the choice of treatment strategy differs based on various factors such as liver function, the patient's condition, the urgency of operating on the primary lesion, and the institution's protocols for dealing with liver metastases and primary lesions. For the primary lesion, it is desirable that surgical removal is selected to improve the quality of life of the patients, because colorectal cancer may cause obstruction, perforation, bleeding, or pain [3]. Additionally it has been reported that stage IV patients who underwent resection of their asymptomatic primary lesions had prolonged median and 2-year survival periods compared with stage IV

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patients who did not undergo resection [3]. However, patients with advanced liver dysfunction due to synchronous liver metastases are not good candidates for surgical removal of the primary lesion. In such circumstances, surgeons and anesthetists usually hesitate to perform surgical removal of the primary lesion, mainly because the patient's condition is too poor to perform surgery and the liver is seen to be the prognosis-limiting factor. As a result insufficient and palliative systemic chemotherapy might be selected without performing surgical removal of the primary lesion in many cases.

With the recent advances in interventional radiology techniques, radiological placements of port-catheter system are increasingly being used in Japan [4, 5]. Repeated hepatic arterial infusion chemotherapy (HAIC) that is performed through an implanted port-catheter system is an effective therapy employed for unresectable advanced liver malignancies [6–8]. In particular, many reports have indicated that HAIC is effective for liver metastases from colorectal cancer [6–8]. It reported that, compared with systemic chemotherapy, HAIC increased the possibility of tumor response and might improve liver function [6].

The purpose of this study was to retrospectively evaluate the safety and efficacy of the initial administration of HAIC through a port-catheter system in patients with advanced liver dysfunction due to synchronous and unresectable liver metastases from colorectal cancer. The aim of HAIC was to improve their clinical condition for the later surgical removal of the primary lesion.

Materials and Methods

Approval from the institutional review board of our hospital and informed consent from all the patients were obtained before performing any procedure.

Patients

Between January 2000 and October 2004, 212 patients with unresectable liver metastases from colorectal cancer underwent radiological placement of port-catheter systems at our institution. In this study, 21 of 212 patients (4 men, 17 women; age 39–77 years, mean 58.6 ± 8.1 years) initially received HAIC through this system to prepare for the surgical removal of the primary lesion later; these patients had liver dysfunction due to synchronous liver metastases. The primary sites of malignancy were as follows: the cecum ($n = 2$), ascending colon ($n = 5$), transverse colon ($n = 3$), sigmoid colon ($n = 7$), and rectum ($n = 4$). With the exception of 1 patient who had a large metastasis in the right lobe of the liver, all patients had diffuse or multiple metastases in both the right and left lobes of the liver. All hepatic lesions were unresectable. All patients had advanced liver dysfunction due to liver metastases, with increased levels of aspartate aminotransferase (AST; mean 110 ± 109 IU/l, range 21–549 IU/l), alanine aminotransferase (ALT; mean 59 ± 43 IU/l, range 17–183 IU/l), total bilirubin (T-BIL; mean 1.0 ± 0.5 mg/dl, range 0.3–2.2 mg/dl), lactate dehydrogenase (LDH; mean 1242 ± 1002 IU/l, range 221–3,870 IU/l), alkaline phosphatase (ALP; mean 874 ± 570 IU/l, range 416–2660 IU/l), and gamma-glutamyl transpeptidase (GTP; mean 393 ± 433 IU/l, range 130–2,023 IU/l). Since the liver dysfunction in these patients had already progressed, we decided to initially administer HAIC instead of the standard systemic chemotherapy in order to improve their liver function. Even in patients with extrahepatic metastases, we initially administered HAIC because we judged that liver metastasis was the prognosis-limiting factor. In 6 of 21 patients, extrahepatic metastases were observed in organs such as the lung ($n = 5$), bone ($n = 1$), and lymph nodes ($n = 1$). Only 1 patient showed evidence of hepatitis B and C virus infection; no other patient had a history of hepatitis. Usually, we consider T-BIL levels >3.0 mg/dl or an Eastern Co-operative Oncology Group performance status [9] of 4 as the exclusion criteria for HAIC administration. However, in this retrospective study, despite conforming to the exclusion criteria, 4 of 212 patients underwent HAIC; these patients were not included in the analysis because these were not planned surgeries.

Port-Catheter System Placement and HAIC

All procedures for the placement of port-catheter systems were performed by interventional radiologists in the angiography suite with the patients under local anesthesia. The procedure was performed as follows. All patients underwent angiography before catheter placement, which was performed using a 5 Fr angiographic catheter (Clinical Supply, Gifu, Japan) inserted from the right femoral artery to allow arterial mapping and to prevent extrahepatic influx of the anticancer agents. The extrahepatic arteries branching from the hepatic artery, such as the right gastric artery, posterior superior pancreatoduodenal artery, and superior duodenal artery, were embolized with microcoils (Tornado; Cook, Bloomington, IN, USA or Trufill; Cordis, Miami Lakes, FL, USA) through a 2.5 Fr microcatheter (Jamiro; Kaneka, Osaka, Japan or Sniper; Clinical Supply, Gifu, Japan) inserted coaxially [10, 11]. In patients with more than two hepatic arteries, these arteries were converted into a single arterial supply by microcoil embolization so that drugs could be distributed to the entire liver using a single indwelling catheter [10]. Next, a 5 Fr angiographic catheter

was inserted from the left subclavian artery and advanced to the common hepatic artery via the celiac artery. Then an indwelling catheter (Anthron P-U catheter; Toray Medical, Tokyo, Japan or W spiral catheter; PIOLAX, Yokohama, Japan) with a side hole was inserted using the catheter-exchange method. The catheter tip was inserted into the deep segment of the gastroduodenal artery so that the side hole was placed into the common hepatic artery. The gastroduodenal artery around the tip of the indwelling catheter was embolized using microcoils and a mixture (1:1.5) of *n*-butyl cyanoacrylate (NBCA; Histoacryl; Braun, Melsungen, Germany) and iodized oil (Lipiodol Ultrafluide; Laboratoire Guerbet, Roissy, France) through a microcatheter inserted coaxially via the 5 Fr angiographic catheter inserted from the right femoral artery. Finally, the proximal end of the indwelling catheter was connected to a port implanted in the subcutaneous pocket created in the left chest wall.

Digital subtraction angiography and CT were performed during injection of contrast medium through the implanted port-catheter system within a few days of implantation to confirm that the catheter was not dislodged and that the entire liver was perfused adequately. Thereafter, HAIC was administered through this system: 1,000 mg/m^2 of 5-fluorouracil (5-FU) weekly by continuous 5 hr infusion [7]. After administration of the chemotherapeutic agent, the implanted port-catheter system was flushed and filled with 2 ml of heparin solution (1,000 IU/ml).

Statistical Analysis

The success rate and the complications of the placement of the port-catheter system were evaluated. After starting HAIC the clinical course, including improvement in liver function tests, performance of surgery, and survival were evaluated. In patients who underwent surgical removal of the primary lesion, the frequency of HAIC administration, time between the placement of the port-catheter system and surgery, details of the surgery, postoperative therapy, and survival were evaluated. The Wilcoxon signed rank test was used to compare the liver functions before surgery with those before starting HAIC. The cumulative survival rate was calculated using the Kaplan-Meier method.

A p value of less than .05 was considered significant.

Results

After placement of the port-catheter system, patients were followed up for a median of 309 days (range 51–998 days).

Placement of the Port-Catheter System

The radiological placement of the port-catheter system was successful in all 21 patients. During and after the procedure, there were no complications such as hematoma, subclavian or vertebral artery thrombosis, infections, hepatic artery occlusions, and catheter malfunctions.

Clinical Course after Starting HAIC

After starting HAIC, no severe adverse events that caused drug loss and treatment postponement or suspension were observed in any of the patients. HAIC was performed a mean of 4.5 ± 3.0 times (range 1–15 times) and the liver function improved in all 21 patients. In particular, the AST, ALT, LDH, ALP, and GTP levels were improved significantly (Table 1). In 19 of 21 patients, curative (n = 18) or palliative (n = 1) surgical removal of the primary lesion was performed. In the remaining 2 patients, although the liver function had improved after HAIC was administered 15 times and 5 times, respectively, extrahepatic metastases in the lung, bone or peritoneum developed rapidly and their performance status worsened. Though systemic chemotherapy was administered with or instead of HAIC afterward, they died 186 and 51 days, respectively, after the placement of port-catheter system; thus, surgery could not be performed.

Among the 19 patients who underwent surgery, HAIC was administered a mean of 3.9 ± 1.8 times (range 1–9 times), and the median period between placement of the

Table 1 Liver function before and after HAIC administration

		Before starting HAIC	After HAIC	p value
AST (IU/l)	Mean	110 ± 109	56 ± 55	
	Range	21–549	21–273	0.0001*
ALT (IU/l)	Mean	59 ± 43	31 ± 22	
	Range	17–183	11–101	0.0005*
T-BIL (mg/dl)	Mean	1.0 ± 0.5	1.2 ± 1.1	
	Range	0.3–2.2	0.3–4.4	0.717
LDH (IU/l)	Mean	1242 ± 1002	551 ± 501	
	Range	221–3870	174–2050	<0.0001*
ALP (IU/l)	Mean	874 ± 570	663 ± 526	
	Range	416–2660	124–2335	0.0046*
GTP (IU/l)	Mean	393 ± 433	207 ± 169	
	Range	130–2023	9–602	0.0061*

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-BIL, total bilirubin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GTP, gamma-glutamyl transpeptidase; HAIC, hepatic arterial infusion chemotherapy

*Significant at $p < 0.05$

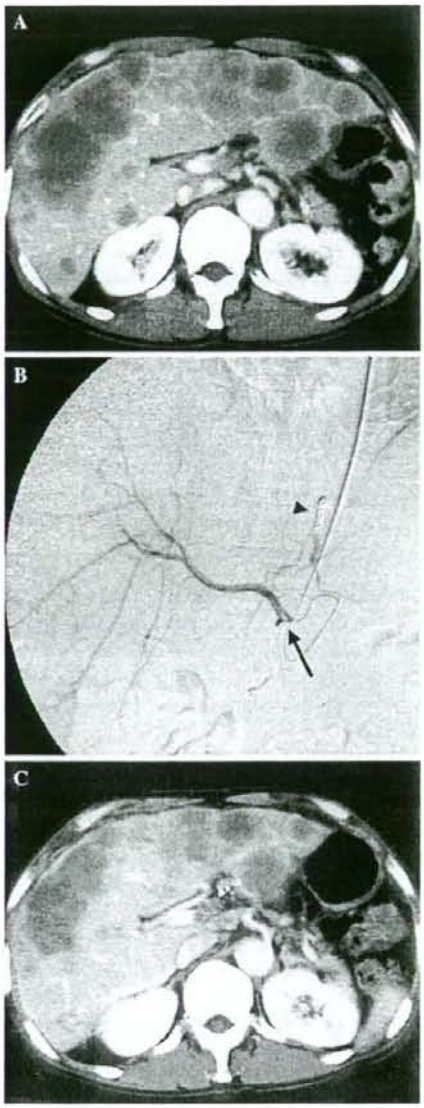

Fig. 2 **A–C.** A 55-year-old man with multiple liver metastases from rectal cancer. **A** Contrast-enhanced CT scan obtained before starting HAIC shows unresectable multiple liver metastases in both the right and left lobes. **B** An arteriogram via the port obtained before starting HAIC shows that all hepatic arteries are well visualized. The catheter tip was inserted into the deep segment of the gastroduodenal artery and embolized using microcoils and a mixture of *n*-butyl cyanoacrylate and iodized oil. The side hole was placed into the common hepatic artery (arrow). The accessory left hepatic artery, which branched from the left gastric artery, was embolized with microcoils (arrowhead) in order to establish hepatic arterial supply from a single vessel. **C** Contrast-enhanced CT scan obtained after five HAIC administrations shows slightly smaller multiple liver metastases. With the exception of T-BIL, the patient's liver function improved (AST improved from 83 to 26 IU/l, ALT improved from 49 to 18 IU/l, LDH improved from 1,155 to 458 IU/l, and ALP improved from 950 to 502 IU/l)

port-catheter system and surgery was 29 days (range 14–68 days). Of 13 patients who had no extrahepatic metastases prior to the surgery, 10 developed extrahepatic metastases. Among 16 of 19 patients, systemic chemotherapy with or instead of HAIC was administered after the surgery.

The overall median survival time of all the patients was 309 days and that of the patients who underwent surgery was 386 days (Fig. 1). At present, 20 patients have died.

A representative case is shown in Fig. 2.

Discussion

Many studies have reported the effectiveness of HAIC administration through a port-catheter system for liver metastases from colorectal cancer [6–8]. In Western countries, it has been reported that HAIC is effective in treating liver metastases; however, it does not improve the prognosis [6]. On the other hand, in Japan, good results have been reported after intermittent hepatic arterial infusion of a high dose of 5-FU: the response rate is reportedly 78% and the median survival time is 25.8 months [7].

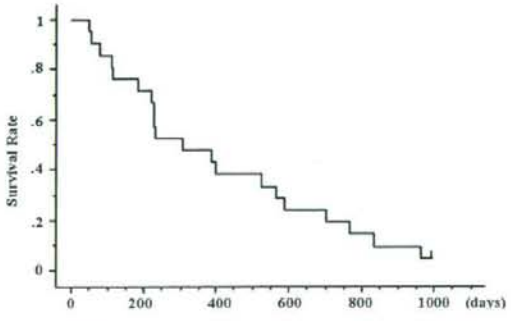

Fig. 1 Overall survival time

In general, systemic chemotherapy is usually selected for colorectal cancer with distant metastases [2]. Recently, the standard regimens such as FOLFILI (5-FU plus leucovorin with oxaliplatin) and FORFOX (5-FU plus leucovorin and irinotecan) are used, and the median survival after FOLFILI and FORFOX has been reported to be 12.6–21.5 months [12]. In many cases, systemic chemotherapy might be the first choice of treatment for patients with primary colorectal cancer and synchronous distant metastases, and we usually select systemic chemotherapy

as an initial therapy for such patients. Although it is doubtful whether the initial HAIC administration is effective in patients who have not undergone any therapy for the primary lesion, HAIC was administered initially in order to improve or control liver metastases. We judged that liver metastasis was the prognosis-limiting factor, because the liver dysfunction in these patients had already progressed due to liver metastases. Additionally, we aim to surgically remove the primary lesion later, if possible, because primary colorectal cancer may cause obstruction, perforation, bleeding, or pain [3]. Based on the results of this study, we believe that initial HAIC administration is effective because, in 19 of 21 patients, surgery was possible after the liver function had been improved by HAIC administration.

In the 19 patients who underwent surgery, HAIC administration was terminated 1 week before surgery to prevent its effect on surgery. The wide range of the frequency of HAIC administration was due to the fact that surgery was not performed until, in the surgeons' opinion, the patient's liver function had improved. We observed that the liver functions before surgery had improved significantly after HAIC administration compared with those before starting HAIC. It has been reported that HAIC has fewer side effects than systemic chemotherapy [13] and, in fact, we observed that surgeries could be performed without any adverse effects arising due to HAIC. We usually consider T-BIL >3.0 mg/dl or a performance status of 4 as the exclusion criteria for HAIC administration because, based on our experience, it is difficult to reduce such liver dysfunction and also improve performance status in patients. Further, the liver dysfunction of such patients may be adversely affected by HAIC administration. Based on our results, there were no severe adverse events after HAIC administration when these exclusion criteria were used for the selection of the candidates. In 2 of 21 patients, although the liver function improved after HAIC administration, surgery could not be performed because they developed extrahepatic metastases in the lung, bone or peritoneum, and their performance status worsened. Unfortunately, we cannot expect HAIC administration to have an anticancer effect on the entire body [7].

There were some limitations in our retrospective study. Firstly, the liver dysfunction of our patients was already advanced; therefore, we hesitated to administer systemic chemotherapy when malignancy was first identified. Secondly, in many patients, other distant metastases were present or developed and systemic chemotherapy was started after the surgery. We could not administer standard systemic chemotherapy such as FOLFILI and FORFOX, and our regimens of systemic chemotherapy were not established, because it is only recently that such standard regimens have been employed in practice in Japan. The survival period might have been prolonged if we had employed the currently used standard systemic chemotherapy.

In conclusion, initial HAIC administration is a safe and efficacious method for improving liver function prior to operative resection of primary colorectal cancer in patients with liver dysfunction due to synchronous and unresectable liver metastases.

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CASE REPORT

Computed tomography and magnetic resonance imaging findings of soft tissue perineurioma

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Abstract Soft tissue perineurioma is an uncommon benign peripheral nerve sheath tumor, although it is the most common subtype of perineuriomas. We present a case of soft tissue perineurioma in the left groin of a 48-year-old man. Precontrast computed tomography showed a homogeneous hypodense mass that showed faint enhancement. The mass appeared with hypointensity on T1-weighted magnetic resonance (MR) images and heterogeneous hyperintensity on T2-weighted MR images. Slight contrast uptake was noted on enhanced T1-weighted MR images with fat suppression. Although these CT and MR imaging findings were nonspecific, the overall imaging features are similar to those of schwannomas.

Key words Perineurioma · Groin · MR imaging · CT

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Introduction

Perineurioma is a rare benign peripheral nerve sheath tumor. It was first described in 1978 by Lazarus and Trombetta on the basis of ultrastructural findings.[1] This tumor is composed of cells resembling those of the normal perineurium. Soft tissue perineurioma is the most common variant among other perineurioma variants. Recent studies have established the histological appearance and clinical behavior of the soft tissue perineurioma. It is usually a well-circumscribed, firm mass with or without spontaneous pain or tenderness.

To the best of our knowledge, imaging findings of soft tissue perineuriomas, including computed tomography (CT) and magnetic resonance imaging (MRI) have not been reported. We report CT and MRI findings of a soft tissue perineurioma with pathological correlation.

Case report

A 48-year-old man presented with a 3-year history of a slowly growing mass and vague discomfort in his left groin. Physical examination revealed a well-delineated, elastic, hard, nontender mass without radiating pain. The tumor was well circumscribed with no fixation of tumor by muscle contraction and no limitation of his left lower thigh motion.

Precontrast CT showed a round, well-delineated mass in the subcutaneous tissue of the left groin, measuring maximally 35 × 30 mm, with homogeneous hypodensity compared with that of muscle (Fig. 1a). CT after intravenous administration of iodinated contrast medium demonstrated unremarkable enhancement (Fig. 1b). The mass was homogeneous with isointensity similar to that

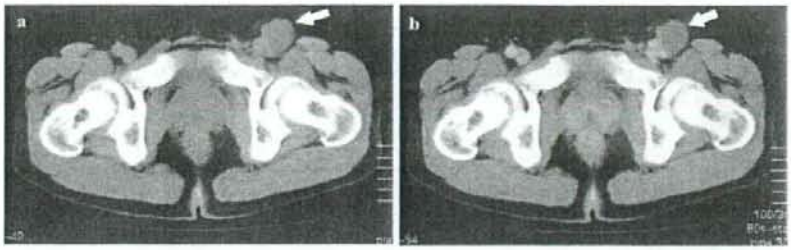

Fig. 1. **a** Precontrast computed tomography (CT) shows a round, well-circumscribed mass (*arrow*) in the left groin with homogeneous hypodensity (mean 20 HU) compared with that of muscle. **b** Contrast-enhanced CT shows homogeneous faint enhancement (mean 36 HU) (*arrow*)

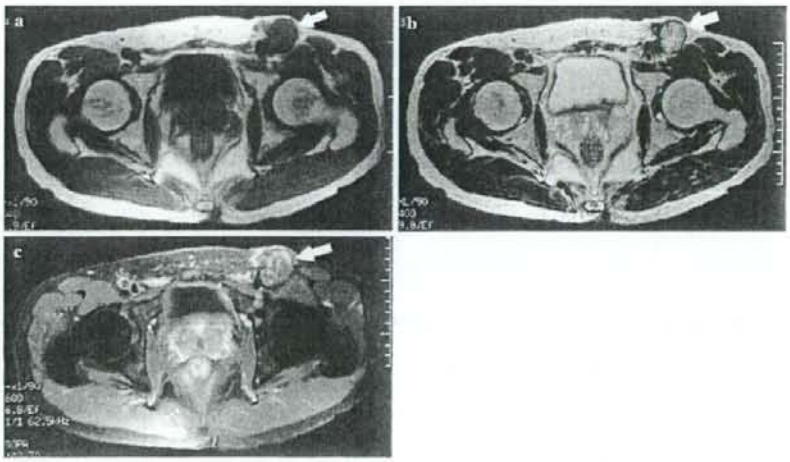

Fig. 2. **a** Axial T1-weighted spin echo (SE) magnetic resonance (MR) images (TR/TE: 540/6 ms) of the tumor shows homogeneous isointensity similar to that of muscle (*arrow*). **b** Axial T2-weighted fast (F)SE MR image shows heterogeneous hyperintensity (TR/effective TE: 4400/99) with marginal hypointensity (*arrow*), suggestive of a capsule or pseudocapsule. **c** Axial gadolinium-enhanced T1-weighted SE MR image (TR/TE: 600/6) with fat suppression shows heterogeneous enhancement (*arrow*)

of muscle on T1-weighted spin echo (SE) MR images (Fig. 2a). On T2-weighted fast spin echo (FSE) MR images, the mass showed heterogeneity by hyperintense signals (Fig. 2b). On T1-weighted SE MR images with fat suppression after intravenous injection of gadolinium contrast medium, the mass showed heterogeneous slight enhancement (Fig. 2c). The margin of the mass was hypointense on all MRI pulse sequences, suggestive of a capsule or pseudocapsule.

The patient underwent an excisional biopsy. The tumor was covered with a fibrous pseudocapsule that was firmly attached to the left femoral vein. Total removal of the tumor with adequate margin from the left femoral vein was difficult, and marginal excision was performed. Grossly, the tumor was firm and well circumscribed, and the cut surface of the tumor was solid, whitish, glistening, and homogeneous in appearance (Fig. 3). There was no hemorrhage, necrosis, cystic change, or invasion to adjacent tissue.

Fig. 3. Gross view of specimen reveals a solid, whitish, glistening, homogeneous appearance. There was no hemorrhage, necrosis, or cystic change

Fig. 4. a Photomicrograph shows spindle cells with curved nuclei and thin, elongated cytoplasmic processes in a myxomatous background. b Tumor cells are immunohistochemically positive for human erythrocyte glucose transporter protein 1

Histological examination revealed spindle cells with curved nuclei and thin, bipolar elongated cytoplasmic processes arranged in lamellae, bundles, and loose whorl patterns in a myxomatous background (Fig. 4a). Immunohistochemically, epithelial membrane antigen (EMA) was diffusely positive, and S-100 protein was negative. In addition, human erythrocyte glucose transporter protein 1 (GLUT1) was diffusely and strongly positive with an intensity similar to that of erythrocytes in tissue sections (Fig. 4b). Additional immunohistochemical staining of MIB-1 was positive in fewer than 1% of the tumor cells. A histological diagnosis of soft tissue perineurioma was made.

After simple excision, there has been no evidence of recurrence or metastasis for 1.5 years.

Discussion

Soft tissue perineurioma is the most common subtype of four perineurioma variants, including intraneural, sclerosing, reticular, and soft tissue perineuriomas.[1–4] Soft tissue perineurioma presents as a painless or painful mass in dermal, subcutaneous, or deep soft tissue with an approximately equal sex distribution. The tumor shows a wide anatomical distribution, with the most common site the lower limb and limb girdle including the groin (44%), followed by the upper limb and limb girdle (23%), trunk (18%), and head and neck (9%). The groin is the most uncommon site in the lower limb and limb girdle group.[2]

The diagnosis requires light microscopic and immunohistochemical examination. Microscopically, the tumor has myxomatous stroma and contains small epithelioid and plump spindle cells with bipolar elongated cytoplasmic processes, as shown in this case. Immunohistochemically, perineurioma cells express vimentin and EMA and lack immunoreactivity for S-100 protein. Immunoreactivity for both GLUT1 and EMA is considered useful for confirming perineurial differentiation.[5,6] In our case, GLUT1 was strongly and diffusely positive, and EMA was positive, a characteristic finding for this tumor.

Among the perineurioma variants, MRI findings of intraneural and sclerosing perineuriomas have been reported. Intraneural perineurioma usually affects the upper extremity in young people and presents as mononeuropathy. The affected nerve or plexus shows enlargement with hyperintensity on T2-weighted images and enhancement after gadolinium administration.[7] Sclerosing perineurioma shows hypointensity on both T2- and T1-weighted images, reflecting abundant collagen and hyalinized stroma. Sclerosing perineurioma has a strong predilection for the digits and palms of young adult men.[8] These two variants of perineuriomas have a predilection for the specific sites and have characteristic imaging findings on MRI.

To the best of our knowledge, CT and MRI findings for soft tissue perineuriomas have not been previously reported in the English-language literature. In our case, CT revealed a homogenously hypodense mass that showed faint contrast uptake. The tumor appeared homogeneously hypointense on T1-weighted images, whereas T2-weighted images showed heterogeneous hyperintensity. Slight contrast uptake was noted on enhanced T1-weighted images with fat suppression. In the present case, the pathological specimen showed myxomatous stroma, which reflected MR signal intensity. These CT and MR imaging findings were nonspecific but may be included in the differential diagnosis of myxoid tumor. The overall imaging features were similar to those of schwannomas.[9]

Magnetic resonance imaging clearly delineated the depth of the tumor and the relation to the vascular and muscular structure, aiding in surgical planning. The tumor was attached to the left femoral vein and was surrounded by a thin pseudocapsule. The fibrous pseudocapsule was hypointense on all MRI pulse sequences, although a fibrous pseudocapsule has not always been noted in soft tissue perineuriomas (23.5%).[2]

In conclusion, although the imaging findings of the current case were nonspecific, the overall imaging features are similar to those of schwannomas.

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ORIGINAL ARTICLE

Computer-aided detection in computed tomography colonography: current status and problems with detection of early colorectal cancer

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Abstract
Purpose. The aim of this study was to evaluate the usefulness of computer-aided detection (CAD) in diagnosing early colorectal cancer using computed tomography colonography (CTC).
Materials and methods. A total of 30 CTC data sets for 30 early colorectal cancers in 30 patients were retrospectively reviewed by three radiologists. After primary evaluation, a second reading was performed using CAD findings. The readers evaluated each colorectal segment for the presence or absence of colorectal cancer using five confidence rating levels. To compare the assessment results, the sensitivity and specificity with and without CAD were calculated on the basis of the confidence rating, and differences in these variables were analyzed by receiver operating characteristic (ROC) analysis.
Results. The average sensitivities for the detection without and with CAD for the three readers were 81.6% and 75.6%, respectively. Among the three readers, only one reader improved sensitivity with CAD compared to that without. CAD decreased specificity in all three readers. CAD detected 100% of protruding lesions but only 69.2% of flat lesions. On ROC analysis, the diagnostic performance of all three readers was decreased by use of CAD.
Conclusion. Currently available CAD with CTC does not improve diagnostic performance for detecting early colorectal cancer. An improved CAD algorithm is required for detecting flat lesions and reducing the false-positive rate.

Key words CT colonography · Computer-aided detection · CAD · Colon cancer · Virtual colonoscopy

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Introduction

Using computed tomography (CT) of the colorectum or CT colonography (CTC) is already a common method for evaluating colorectal diseases in Western countries. Although a number of screening techniques are available for patients/physicians to detect colorectal cancer (e.g., fecal occult blood testing, flexible sigmoidoscopy, barium enema, colonoscopy), CTC is considered an evolving technique for screening. This trend has been promoted with the advent of multidetector row CT (MDCT). The utility of CTC for detecting colon polyps has been confirmed in previous reports,[1,2] and the development of diagnostic systems using MDCT is advancing. In addition, much attention has been paid to research on the application of a CAD scheme for detection of colorectal polyps during CTC screening.[3-5]

On the other hand, the importance of detecting early colorectal carcinoma (ECC), especially that of the flat type identified with colonoscopy, has been acknowledged gradually by physicians worldwide.[6-9] To our knowledge, however, no specific CAD scheme have been developed, nor has the detection of these kinds of lesions in CTC been investigated. To make CTC practical for colorectal screening, we believe that a CAD scheme for detecting ECCs needs to be evaluated. In this study, we examined the performance of commercially available CAD software in terms of the detection of ECCs via an observer performance study.

Materials and methods

Patients

This study was conducted in accordance with the amended Helsinki Declaration, and all patients provided informed consent.

Thirty patients with histologically proved ECC were enrolled in this retrospective study. The patients consisted of 20 men and 10 women with an age range of 43–83 years (median 64.8 years). All patients underwent preoperative CTC immediately following colonoscopy in our hospital during the period from July 2006 to November 2006. Colonoscopy was conducted after the standard bowel preparation with up to 2 l of a polyethylene glycol–electrolyte solution.

Endoscopic and/or surgical resection was performed in all patients (19 endoscopic, 10 surgical, 1 both endoscopic and surgical). The pathological diagnosis on resected specimens was confirmed in respective cases. All colon tumors were initially diagnosed by colonoscopy, and the presence and location of the lesions were confirmed based on CT examination. The lesion was initially selected as an ECC if its diagnosis was proved to be T1 by the final pathology study. Next, a lesion was defined as ECC when the pathology of the resected specimen was limited to within the mucosa or showed submucosal invasion.[10] The pathology of the severity of submucosal invasion was defined as sm1 (minute invasion), sm2 (moderate invasion), or sm3 (massive invasion).

A consensus panel of two radiologists who had examined the patients was employed to characterize all lesions in terms of their size and endoscopic morphology on the basis of all available evidence. The radiologists were experts on CTC diagnosis and were aware of all clinical information on the patients, such as endoscopic features and/or pathological findings obtained from biopsy specimens. During the colonoscopy, the colonoscopists reported the size and locations of all lesions identified. In addition, the endoscopic morphology for each lesion was documented using standard criteria.[10] All lesions were classified as "protruding" or "flat" based on the endoscopic findings. According to the "General rules for clinical and pathological studies on cancer of the colon, rectum, and anus," there are polypoidal and nonpolypoidal subtypes of superficial lesions. The polypoidal subtype protrudes above the surrounding mucosa. The nonpolypoidal subtypes include lesions with a small variation of the surface (slightly elevated, flat, slightly depressed) and excavated lesions. In this study, "protruding" and "flat" were determined when the lesions were classified as polypoidal or nonpolypoidal, respectively.

MDCT image acquisition

MDCT scans were performed with a 64 multidetector row CT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). The scan range was from the abdomen to the pelvis, with the following parameters: 120 kV, 200–400 mA with automatic exposure control, 64 rows × 0.5 mm collimation and helical pitch 53 (pitch factor 0.828). As pretreatment, anticholinergic drugs were injected intravenously immediately before each examination, and gas insufflation was performed via the anus with an automated CO_2 insufflator (Protocol; E-Z-EM, Lake Success, NY, USA).

All patients received intravenous contrast medium for staging. A total of 150 ml of contrast medium (Omnipaque 300 mg I/ml; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was administered intravenously with an autoinjector at a rate of 3.0 ml/s. The scan delay was set at 50 s after the injection of contrast medium. Images in prone and supine positions were acquired for each patient. The order of each patient's positions was decided according to the locations of the lesions based on endoscopy reports. In the case of rectal cancer, the first position was supine and the second was prone. On the other hand, when the lesion was located in the cecum to sigmoid colon, the first position was prone.

CAD system

For primary two-dimensional reading, study data were loaded into a workstation equipped with ColonCAD 3.1 software (Medicsight PLC, London, UK). The software permitted scrollable supine and prone two-dimensional transverse images to be displayed adjacently in the upper half of the screen and three-dimensional images to be located in the lower half of the screen. The CAD software was designed to highlight potential polyps to aid radiologists in detecting suspected lesions. The software

segmented the colon based on the CT data set and then determined the inherent sphericity of each raised object in the colonic lumen. A suspected object detected on the basis of the sphericity analysis was then circled in red on the transverse two-dimensional images. After clicking for a detailed three-dimensional display shown in the lower half of the screen, the red circle turned to green.

The performance of the CAD system was evaluated in terms of sensitivity and the number of false-positives per patient for all cases as well as for cases with flat polyps and those with protruding polyps.

Observer study

To evaluate the radiologists' performance for the detection of ECCs without and with CAD software, we employed receiver operating characteristic (ROC) analysis.[11] In the ROC study, the CTC images were interpreted independently by three gastrointestinal radiologists, one with 2 years' experience diagnosing CTC (reader A) and the other two with 4 years' experience (readers B and C). They were blinded to the results of the conventional colonoscopy and CTC and all clinical information on the patients. Images were interpreted twice, first without CAD and then with CAD, at 1-week intervals. The CTC images for one patient were separated into six segments of the colon (i.e., rectum, sigmoid colon, descending colon, transverse colon, ascending colon, cecum) based on the CT scan coordinates (on both prone and supine images). In the observer study, the readers were asked to indicate their confidence rating (CR) for the presence of a polyp or cancer in each segment by using CTCs obtained in both the supine and prone positions. We assumed that each segment was one sample for the ROC analysis; thus, there were 30 positive segments with a confirmed polyp and 150 negative segments with no polyps for the 30 sets of patient image data. In none of the cases were there two or more lesions in a segment. In addition, if a reader believed that there were two or more lesions in a segment, the reader assigned his or her CR for one lesion where he or she had maximum confidence in its presence. A scale of five CRs was used for each segment: 1, definitely absent; 2, probably absent; 3, possibly absent; 4, possibly present; 5, definitely present.

Agreement of confidence ratings for each case among the three readers was estimated using Fleiss's kappa statistics.[12] To evaluate the observers' performance for detecting ECCs without and with CAD, the sensitivity and specificity were calculated for each reader. In this study, an observer's response was considered negative when the confidence rating provided was 3 or less and positive at 4 or more.

A beneficial or detrimental effect due to the use of CAD was evaluated in terms of the difference between two CRs without and with CAD. For example, when the CR obtained by use of CAD was larger than that without CAD for a positive segment, we deemed that the reader was affected beneficially by CAD. On the other hand, when the CR obtained using CAD was larger than that without CAD for a negative segment, we deemed that the reader was affected detrimentally by CAD. In the same manner, a decrease in the CRs for positive and negative segments was considered detrimental and beneficial, respectively.

Statistical analysis

The statistical significance of the difference in the area under the ROC curve (AUC) between observer readings without and with CAD was tested using the Dorfman-Berbaum-Metz method,[13] which included both reader variation and case sample variation by means of an analysis of variance (ANOVA) approach. The statistical significance of the difference in sensitivities between radiologists without and with CAD and in the number of cases between a beneficial and a detrimental effect of CAD was estimated with use of Student's paired t-test for the three readers. In general, $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Lesions

Among the 30 cases, a total of 30 ECCs were confirmed by the consensus panel. As is the usual clinical practice in our hospital, all synchronous polyps >5 mm were removed by the colonoscopist. For the purpose of this study, we excluded the residual polyps from an evaluation subject. No advanced cancer was present in any of the cases. Of the 30 lesions, 7 were located in the rectum, 7 in the sigmoid colon, 3 in the descending colon, 2 in the transverse colon, 6 in the ascending colon, and 5 in the cecum. There were 13 (43.3%) flat lesions and 17 (56.7%) protruding lesions. There were 19 (63.3%) lesions with intramucosal (m) or sm1 invasion and 11 (36.7%) lesions with sm2 or sm3 invasion. Based on the morphology, among the flat lesions, 9 were rated m-sm1 and 4 were sm2–3. Among the protruding lesions, 10 were m-sm1 and 7 were sm2–3. The mean diameter of the flat lesions was 34.7 mm (range 14–70 mm), and that of protruding lesions was 39.8 mm (range 20–70 mm). No significant size difference was found between flat and protruding lesions (unpaired t-test).

CAD performance

Of the 30 ECC lesions, 26 (86.7%) were identified correctly by CAD (Table 1). The numbers of identified ECCs based on lesion size were as follows: 4 of 7 cases (57.1%) in which the lesion was 11–20 mm (a relatively small number) and 22 of 23 cases (95.6%) in which it was ≥21 mm. In terms of polyp types, all protruding-type lesions were detected (17/17, 100%), whereas only 9 of 13 flat lesions were detected (69.2%). Figure 1 shows a protruding cancer lesion was identified by CAD. There was a slight difference between the detection rates of two invasion-depth groups: m and sm1 (89.5%) versus sm2 and sm3 (81.8%).

The four lesions that CAD did not detect were all flat lesions. Figure 2 shows a flat lesion was not detected by CAD with CT colonography. The characteristics of these lesions are listed in Table 2. Two of the four cases had sm2 and sm3 in-depth invasion.

There were 514 false-positive findings for lesions detected by CAD analysis (Fig. 3). The average number of false-positives per patient was 17.1 (range 4–39).

Table 1. Performance of CAD in detection of 30 polyps

Parameter	Data
No. of polyps detected	26/30 (86.7%)
No. of FPs	514 (17.1/case)
Lesion size	
11–20 mm	4/7 (57.1%)
>20 mm	22/23 (95.7%)
Morphology	
Flat	9/13 (69.2%)
Protruding	17/17 (100%)
Invasion depth	
m+sm1	17/19 (86.7%)
sm2+sm3	9/11 (86.7%)

CAD, computer-aided detection; FPs, false-positives

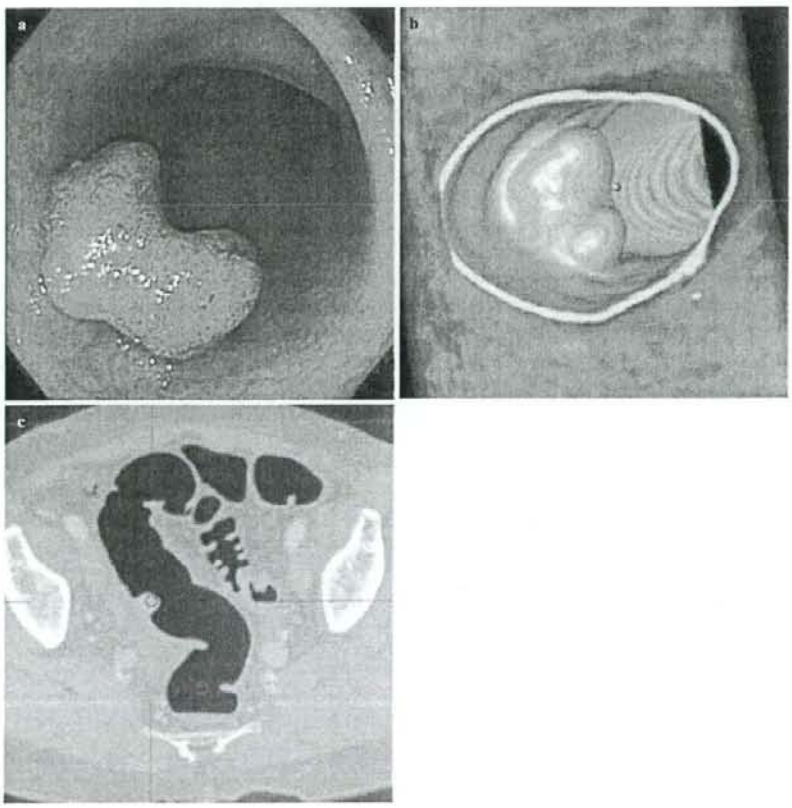

Fig. 1. **a** Conventional colonoscopy revealed a protruding cancer lesion in the upper rectum of a 60-year-old woman. **b, c** The lesion was identified by CAD in an axial image (**b**) and a virtual colonoscopic image (**c**)

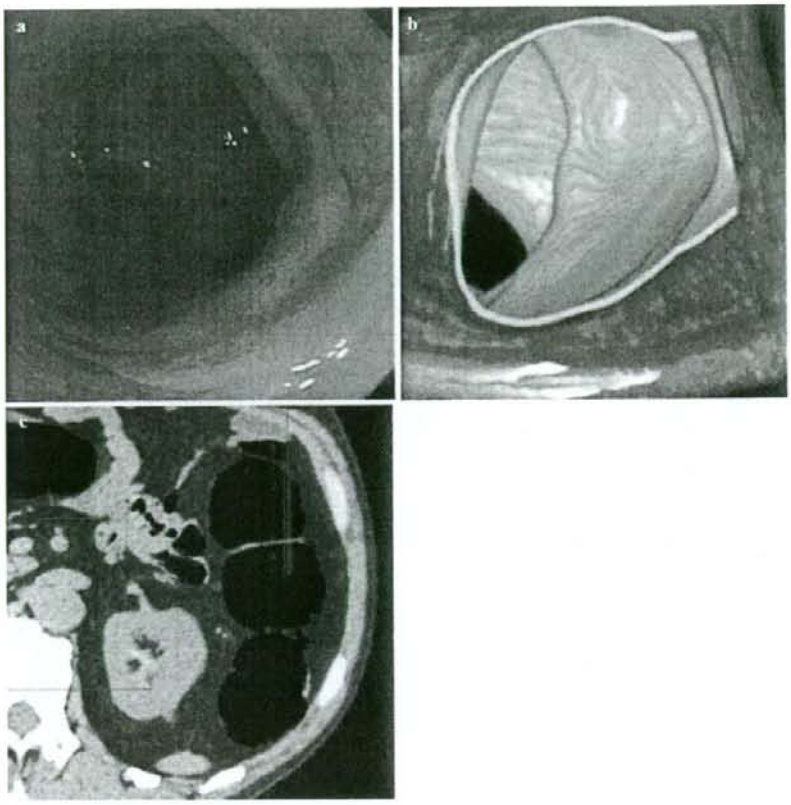

Fig. 2. **a** Conventional colonoscopy revealed a flat lesion in the descending colon. **b**, **c** Although it was not detected by CAD with CT colonography (**b**), the lesion, which caused thickening of the colonic wall (**c**), was identified retrospectively on the axial image

Table 2. Characteristics of four lesions undetected by CAD

Morphology	Segment	Size (mm)	Depth of invasion
Flat	Rectum	34	m
Flat	Sigmoid	14	sm3
Flat	Descending	19	m
Flat	Cecum	20	sm2

Reader performance with and without CAD

The agreement of CRs rated for the 180 colon segments by the three readers without and with CAD was considered "fair." Fleiss's kappa statistic was 0.372 and 0.352, respectively.

The average sensitivities for the detection of 30 ECCs without and with CAD for the three readers were 81.6% (24.3/30) and 75.6% (22.7/30), respectively, as shown in Table 3. Among the three readers, only reader B improved his or her sensitivity with CAD (83.3%) compared to that without CAD (80.0%). There was

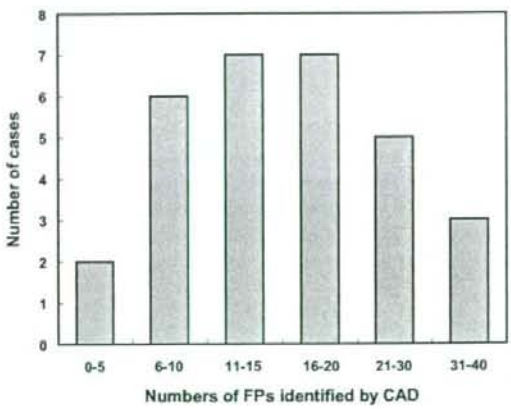

Fig. 3. Number of cases for each group versus the number of false-positive results (*FPs*) identified by computer-aided detection (*CAD*)

Table 3. Sensitivity, specificity, and AUC for the detection of polyps without and with CAD

CAD	Sensitivity ($n = 30$)	Specificity ($n = 150$)	AUC
Reader A			
(−)	24 (80.0%)	146 (97.3%)	0.897
(+)	19 (63.3%)	139 (92.7%)	0.879
Reader B			
(−)	24 (80.0%)	142 (94.7%)	0.951
(+)	25 (83.3%)	140 (93.3%)	0.927
Reader C			
(−)	25 (83.3%)	144 (96.0%)	0.983
(+)	24 (80.0%)	141 (94.0%)	0.949
Mean			
(−)	24.3 (81.1%)	144 (96.0%)	0.944
(+)	22.7 (75.6%)	140 (93.3%)	0.918

AUC, area under the receiver operating characteristic curve; (−), without CAD; (+), with CAD

no statistically significant difference between the average sensitivities obtained without and with CAD ($P = 0.44$). In terms of the diagnostic accuracy for identifying 150 negative segments correctly as negative, the average specificity was decreased from without CAD (144/150, 96.0%) to with CAD (140/150, 93.3%). Although all readers decreased their specificities by using CAD, there was no statistically significant difference ($P = 0.12$).

Figure 4 illustrates average ROC curves for the three readers in diagnosing 30 positive segments with polyps and 150 negative segments with no polyps. As shown in Fig. 4 and Table 3, the average AUC for the three readers was also decreased by using CAD, from 0.944 to 0.918, and there was a statistically significant difference between AUCs obtained without and with CAD ($P = 0.02$).

Figure 5 indicates the beneficial and detrimental effects of using CAD for the three readers affected. There were more detrimental effects after using CAD than beneficial effects, but there was no statistically significant difference between the number of cases with beneficial and detrimental effects of CAD ($P = 0.22$).

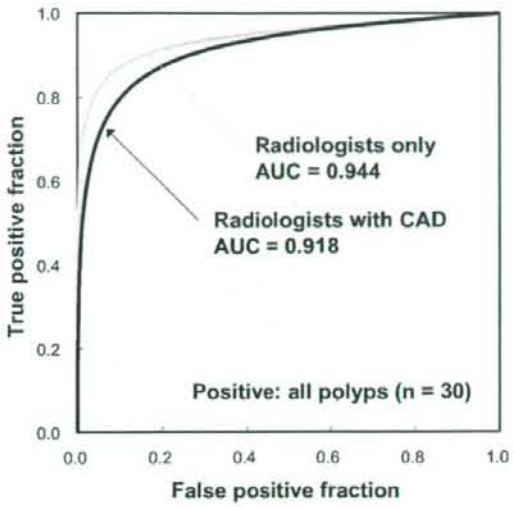

Fig. 4. Average receiver operating characteristic (ROC) curves for the detection of early colorectal carcinomas obtained by three readers without CAD and with CAD output. *AUC*, area under the curve

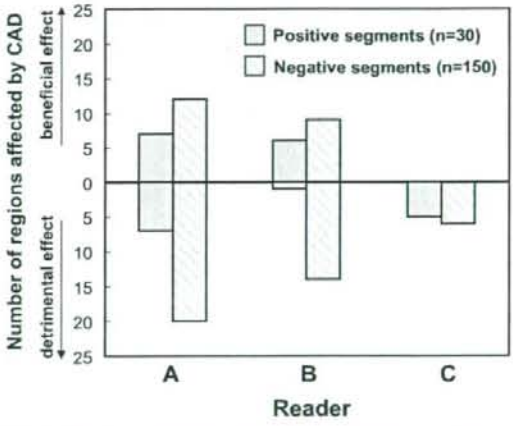

Fig. 5. Number of cases with beneficial and detrimental effects of using CAD

Discussion

Enhanced CT capability with the appearance of MDCT has made CTC a useful tool for diagnosing colon disease. A number of studies have shown an excellent capability of CTC to detect colon polyps,[14–16] and CTC has been recognized as an effective option for colon screening.[17,18] The development of CAD has progressed and is making the best use of digital CT images; moreover, research is underway on the automatic detection of colon polyps. Prior research suggested that the concomitant use of CTC and CAD would increase sensitivity and could shorten the reading time for diagnosing colonic lesions.[19] In addition, some studies have reported the effectiveness of CAD in the evaluation of lesions.[20,21] Colonic cancer lesions, compared to colon polyps, were easier to recognize grossly because of their size and the accompanying wall hypertrophy, giving CAD great potential for detecting these lesions. However, CAD systems have been