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.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM (2004) GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. IARC CancerBase no. 5, version 2.0. IARC Press, Lyon, France
2. Alexander HR, Kemeny NE, Lawrence TS (2000) Metastatic cancer to the liver. In: DeVita VT (ed) Cancer, 7th edn. Williams & Wilkins, Baltimore, pp 2353–2368
3. Ruo L, Gougoutas C, Paty PB, et al. (2003) Elective bowel resection for incurable stage IV colorectal cancer: Prognostic variables for asymptomatic patients. J Am Coll Surg 196:722–728
4. Tanaka T, Arai Y, Inaba Y, et al. (2003) Radiologic placement of side-hole catheter with tip fixation for hepatic arterial infusion chemotherapy. J Vasc Interv Radiol 14:63–68
5. Yamagami T, Iida S, Kato T, et al. (2002) Using *n*-butyl cyanoacrylate and the fixed-catheter-tip technique in percutaneous implantation of a port-catheter system in patients undergoing repeated hepatic arterial chemotherapy. AJR Am J Roentgenol 179:1611–1617
6. Meta-Analysis Group in Cancer (1996) Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst 88:252–258
7. Arai Y, Inaba Y, Takeuchi Y, et al. (1997) Intermittent hepatic arterial infusion of high-dose 5FU on a weekly schedule for liver metastases from colorectal cancer. Cancer Chemother Pharmacol 40:526–530
8. Link KH, Sunelaitis E, Kornmann M, et al. (2001) Regional chemotherapy of nonresectable colorectal liver metastases with mitoxantrone, 5-fluorouracil, folinic acid, and mitomycin C may prolong survival. Cancer 92:2746–2753
9. Oken MM, Creech RH, Tormey DC, et al. (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655
10. Arai Y, Inaba Y, Takeuchi Y (1997) Interventional techniques for hepatic arterial infusion chemotherapy. In: Castaneda-Zuniga WR (ed) Interventional radiology, 3rd edn. Williams & Wilkins, Baltimore, pp 192–205
11. Inaba Y, Arai Y, Matsueda K, et al. (2001) Right gastric artery embolization to prevent acute gastric mucosal lesions in patients undergoing repeat hepatic arterial infusion chemotherapy. J Vasc Interv Radiol 12:957–963
12. Kelly H, Goldberg RM (2005) Systemic therapy for metastatic colorectal cancer: Current options, current evidence. J Clin Oncol 23:4553–4560
13. Collins JM (1984) Pharmacokinetic rationale for intra-arterial therapy. In: Howell SB (ed) Intra-arterial and intracavitary cancer chemotherapy. Martinus Nijhoff, Boston, pp 1–10

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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

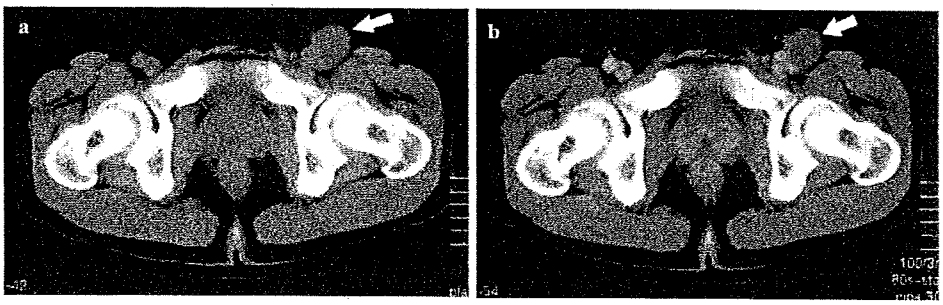

Fig. 1. **a** Precontrast computed tomography (CT) shows a round, well-circumscribed mass (*arrow*) in the left groin with homogeneous hypodensity (mean 20 HU) compared with that of muscle. **b** Contrast-enhanced CT shows homogeneous faint enhancement (mean 36 HU) (*arrow*)

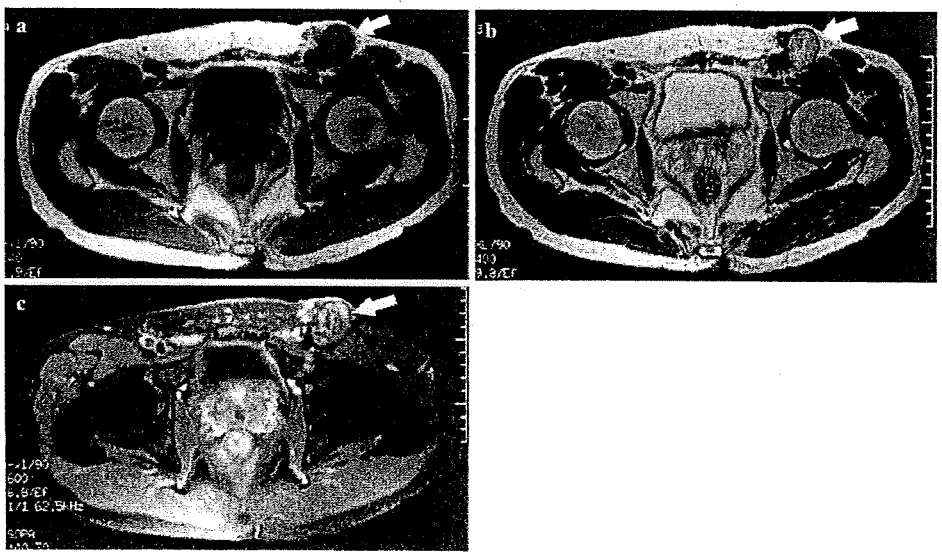

Fig. 2. **a** Axial T1-weighted spin echo (SE) magnetic resonance (MR) images (TR/TE: 540/6 ms) of the tumor shows homogeneous isointensity similar to that of muscle (*arrow*). **b** Axial T2-weighted fast (F)SE MR image shows heterogeneous hyperintensity (TR/effective TE: 4400/99) with marginal hypointensity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

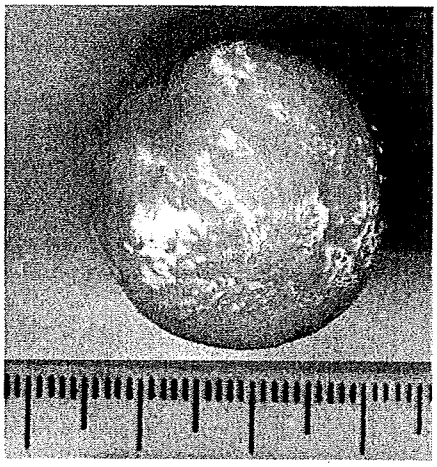

Fig. 3. Gross view of specimen reveals a solid, whitish, glistening, homogeneous appearance. There was no hemorrhage, necrosis, or cystic change

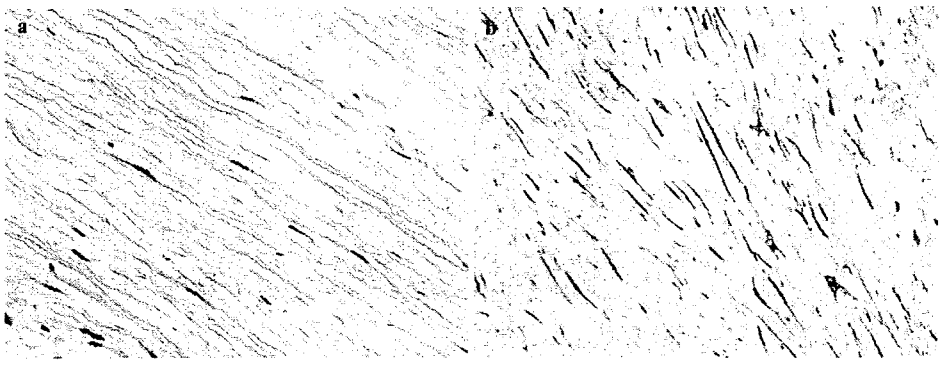

Fig. 4. **a** Photomicrograph shows spindle cells with curved nuclei and thin, elongated cytoplasmic processes in a myxomatous background. **b** Tumor cells are immunohistochemically positive for human erythrocyte glucose transporter protein 1

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.

References

1. Lazarus SS, Trombetta LD. Ultrastructural identification of a benign perineurial cell tumor. Cancer 1978;41:1823–9.
2. Hornick JL, Fletcher CD. Soft tissue perineurioma: clinicopathologic analysis of 81 cases including those with atypical histologic features. Am J Surg Pathol 2005;29:845–58.
3. Fetsch JF, Miettinen M. Sclerosing perineurioma: a clinicopathologic study of 19 cases of a distinctive soft tissue lesion with a predilection for the fingers and palms of young adults. Am J Surg Pathol 1997;21:1433–42.
4. Brock JE, Perez-Atayde AR, Kozakewich HP, Richkind KE, Fletcher JA, Vargas SO. Cytogenetic aberrations in perineurioma: variation with subtype. Am J Surg Pathol 2005;29: 1164–9.
5. Yamaguchi U, Hasegawa T, Hirose T, Fugo K, Mitsuhashi T, Shimizu M, et al. Sclerosing perineurioma: a clinicopathological study of five cases and diagnostic utility of immunohistochemical staining for GLUT1. Virchows Arch 2003;443: 159–63.
6. Hirose T, Tani T, Shimada T, Ishizawa K, Shimada S, Sano T. Immunohistochemical demonstration of EMA/GLUT1-positive perineurial cells and CD34 positive fibroblastic cells in peripheral nerve sheath tumors. Mod Pathol 2003;16:293–8.
7. Simmons Z, Mahadeen ZI, Kothari MJ, Powers S, Wise S, Towfighi J. Localized hypertrophic neuropathy: magnetic resonance imaging findings and long-term follow-up. Muscle Nerve 1999;22:28–36.
8. Miyake M, Tateishi U, Maeda T, Arai Y, Seki K, Hasegawa T, et al. Sclerosing perineurioma: tumor of the hand with a short T2. Skeletal Radiol 2006;35:543–6.
9. Pilavaki M, Chourmouzi D, Kiziridou A, Skordalaki A, Zarampoukas T, Drevelengas A. Imaging of peripheral nerve sheath tumors with pathologic correlation: pictorial review. Eur J Radiol 2004;52:229–39.

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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

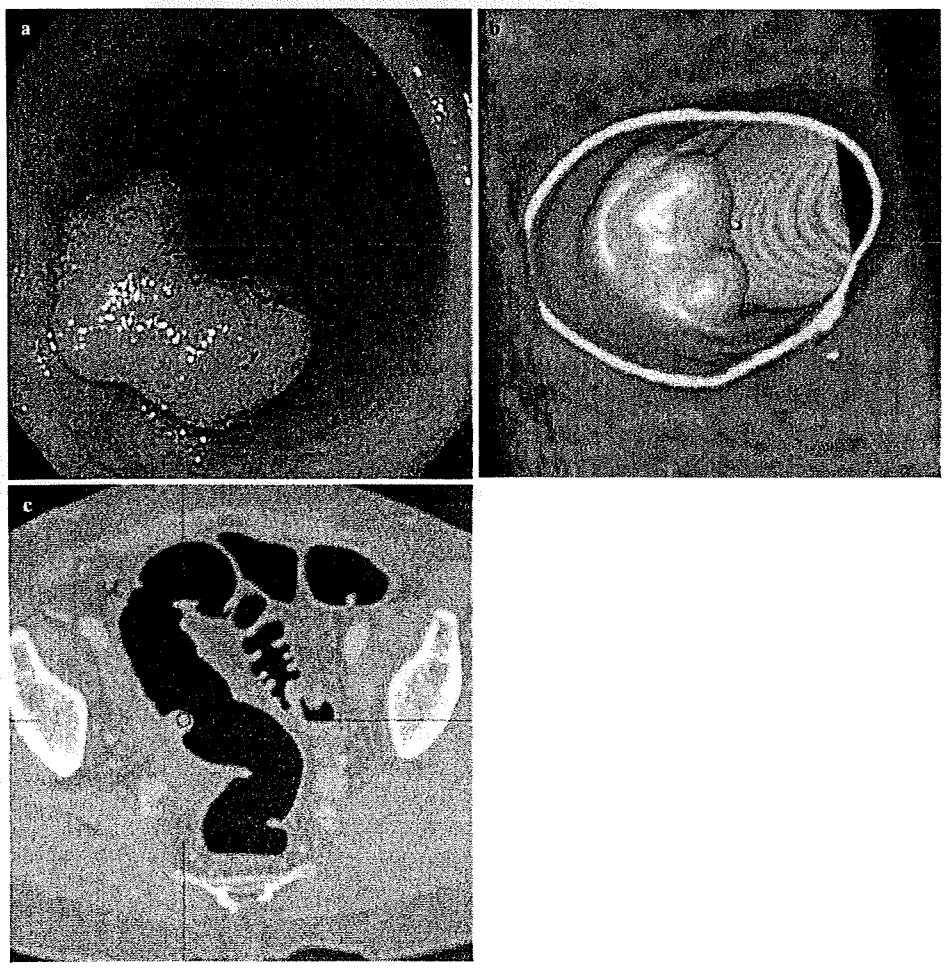

Fig. 1. **a** Conventional colonoscopy revealed a protruding cancer lesion in the upper rectum of a 60-year-old woman. **b, c** The lesion was identified by CAD in an axial image (**b**) and a virtual colonoscopic image (**c**)

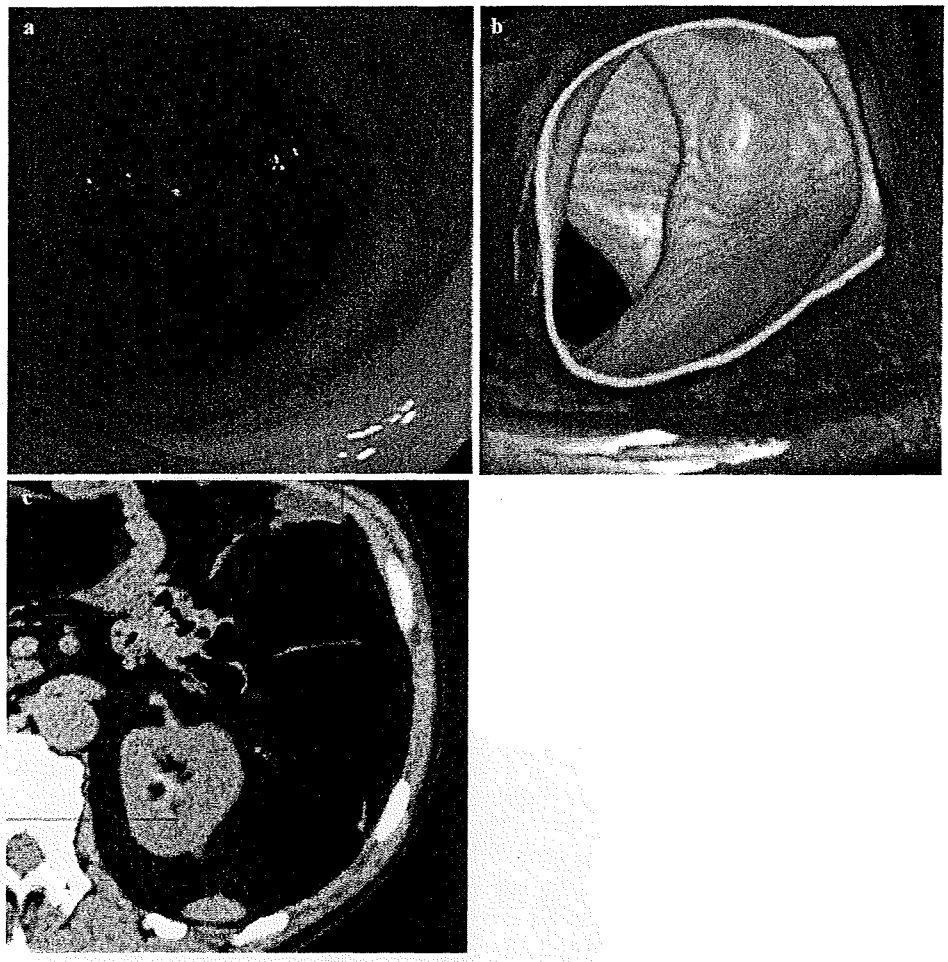

Fig. 2. **a** Conventional colonoscopy revealed a flat lesion in the descending colon. **b, c** Although it was not detected by CAD with CT colonography (**b**), the lesion, which caused thickening of the colonic wall (**c**), was identified retrospectively on the axial image

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

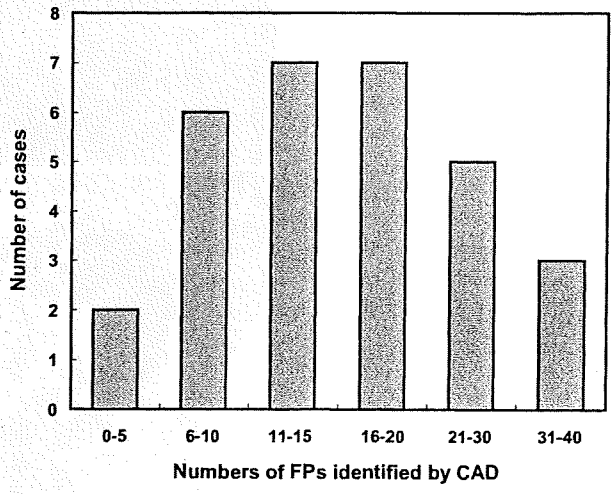

Fig. 3. Number of cases for each group versus the number of false-positive results (*FPs*) identified by computer-aided detection (*CAD*)

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 ($P = 0.22$).

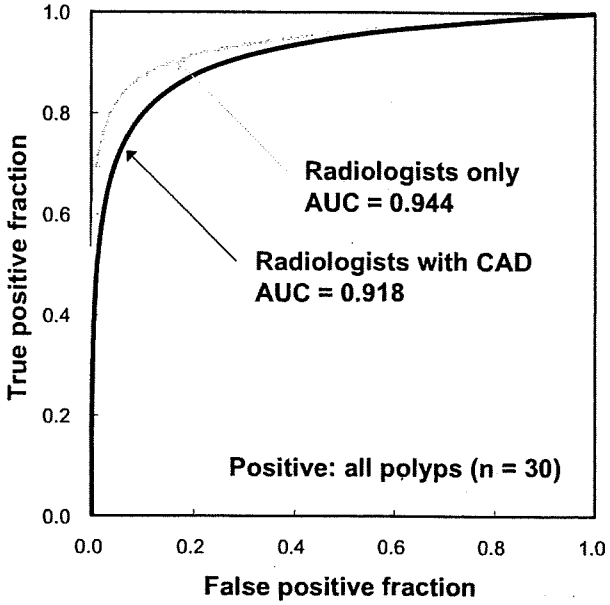

Fig. 4. Average receiver operating characteristic (ROC) curves for the detection of early colorectal carcinomas obtained by three readers without CAD and with CAD output. *AUC*, area under the curve

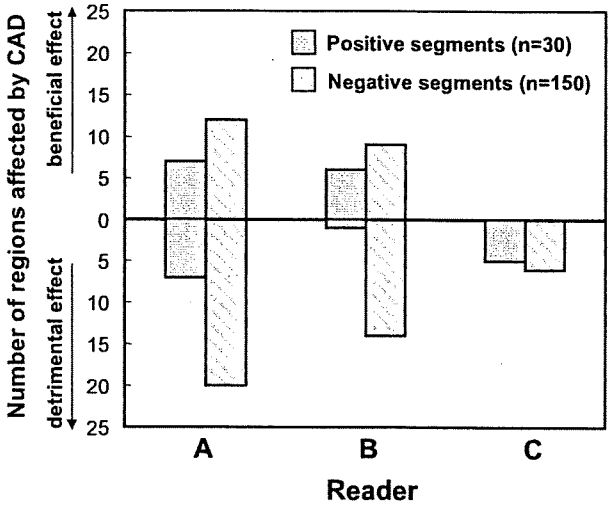

Fig. 5. Number of cases with beneficial and detrimental effects of using CAD

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

developed principally for the detection of colon polyps, and few studies have focused on the detection of ECCs, including flat lesions. In recent years, detection of colon cancers in their early stages, especially lesions of the flat type, was considered to be important in Japan and Western countries. Therefore, evaluation of a CAD protocol in terms of the clinical utility for the detecting early lesions, particularly those of invasive cancer, would be valuable.

The results of this study include 100% sensitivity of CAD for protruding lesions and low sensitivity (69.2%) for flat lesions. Previous investigations reported poor performance of both CTC[22–25] and CAD[26–28] in detecting flat lesions, and our study confirmed these results. The conventional CAD programs were developed mainly for detecting protruding polyps. The four lesions that were not detected by CAD in this study were all flat, suggesting the need for improved CAD diagnostic performance for flat lesions. With conventional CAD, lesions are recognized on the basis of the sphericity of the object protruding from the colonic lumen. In this study, we used the sphericity setting that is effective in diagnosing colon polyps with well-balanced sensitivity and low false-positive rates.[29] The diagnostic performance for flat lesions may be improved by modification of the presently used sphericity setting.

In this study, only one reader demonstrated increased sensitivity when using CAD, whereas the other two showed decreased sensitivity. However, the difference in sensitivity was not significant. Previous studies reported the effectiveness of CAD in detecting polyps, but our study did not prove its effectiveness in detecting ECCs. Moreover, in the ROC analysis, all three readers demonstrated inferior diagnostic performance with CAD, and there was a statistically significant difference. Although the sensitivity of CAD for the detection of ECCs (86.7%) was relatively high, an average of 4.0 ECCs were considered "nonactionable,"[30] which indicated that the lesion was identified correctly by CAD but was not recognized correctly as a lesion by the reader. Therefore, we believe that the clinical utility of CAD can be increased by familiarizing the readers with the use of CAD.

CAD had an average false-positive number of 17.1, which might contribute to the inferior diagnostic performance. Fenton et al.[31] reported that CAD increased the number of false-positive diagnoses on mammograms, leading to increased recall and biopsy rates. Therefore, reducing CAD false-positive rates would be required for improving the diagnostic performance.

All three readers showed fair agreement in their CRs for the detection of ECCs with and without CAD, indicating a possible influence of the readers' experience with CTC image reading. Mang et al.,[20] in a study on image reading by two expert radiologists and two nonexperts, reported that the sensitivity for detecting colon polyps was increased with CAD, with the increase being significant for the two nonexperts. In our study, reader A showed beneficial effects from using CAD for seven segments with a lesion, suggesting the usefulness of CAD for nonexperts. However, reader A also showed detrimental effects of CAD for 7 segments with a lesion and for 20 segments without lesions. These results suggest that nonexperts could receive some benefit from CAD, but their insufficient experience in the reading of CTC might affect their diagnostic performance.[32–34] As Halligan et al.[21] mentioned, the improvement in diagnostic accuracy by using CAD is insufficient to recommend that CAD can substitute for adequate training for readers who are relatively inexperienced.

Our study has potential limitations. Only a small number of patients were included. Although the number of samples for the ROC study was not so small (30 positive and 150 negative samples), each of the six colonic segments, which were divided from one case, was considered to be clustered in terms of statistical issues. For example, the reader's attention for the detection of a lesion might be diverted when he or she found lesions in the same patient. Because ROC analysis assumed that each sample was independent from others, it was considered to be a bias to use clustered data in the ROC study.

There was a 1-week interval between the two readings without and with CAD. Generally, the interval of 1 week for two readings is relatively small if the first reading can provide additional information to readers at the second reading. However, in the observer performance study for evaluating CAD, it was demonstrated that two independent and sequential readings without and with CAD were thought to be comparable in terms of the radiologists' performance obtained by the ROC study.[35] Because the first reading without CAD did not provide any additional information for the second reading, we believe that the short length of the intervals between the two readings caused no bias in this study.

We used conventional ROC analysis in this observer study, rather than free-response ROC analyses,[36] because we wanted to the minimize the radiologists' tasks in the observer study. In addition, ROC analysis can provide reliable estimates of the statistical significance of differences between two conditions (i.e., without and with the CAD output) when multiple readers were employed in a study.[13] However, it should be noted that this observer study involved several limitations that were well understood to be limitations of conventional ROC analysis.[37] The scoring of true-positive responses on each image by

radiologists did not take into account the location of nodules when the ROC curves were estimated, so some false-positive responses in actual ECC cases could be counted as true-positive responses. Furthermore, radiologists were allowed to indicate only one CR on each segment, so additional false-positive responses and/or true-positive responses might have been obtained if radiologists were allowed to indicate two or more lesions in one segment. Although almost all observer performance studies that employ ROC analysis have been done under these limitations, their results are generally considered useful.

Conclusion

The present CAD programs do not contribute to improved diagnostic accuracy for the detection of ECCs on CTC. The present CAD analysis algorithm demonstrated an inferior performance in detecting flat-type lesions compared to that for protruding lesions. Further investigation is required to clarify the specific features of flat lesions that would improve the performance of the CAD algorithm. Moreover, the reader's experience in diagnostic CTC reading would be considered in the evaluation of the clinical utility of CAD for detecting ECCs.

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References

1. Halligan S, Altman DG, Taylor SA, Mallett S, Deeks JJ, Bartram CI, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237:893–904.
2. Sosna J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. AJR Am J Roentgenol 2003;181:1593–8.
3. Bielen D, Kiss G. Computer-aided detection for CT colonography: update 2007. Abdom Imaging 2007;32:571–81.
4. Bogoni L, Cathier P, Dundar M, Jerebko A, Lakare S, Liang J, et al. Computer-aided detection (CAD) for CT colonography: a tool to address a growing need. Br J Radiol 2005;78(Spec. No. 1):S57–62.
5. Summers RM, Jerebko AK, Franaszek M, Malley JD, Johnson CD. Colonic polyps: complementary role of computer-aided detection in CT colonography. Radiology 2002; 225:391–9.
6. Soetikno R, Friedland S, Kaltenbach T, Chayama K, Tanaka S. Nonpolypoid (flat and depressed) colorectal neoplasms. Gastroenterology 2006;130:566–76.
7. Saitoh Y, Waxman I, West AB, Popnikolov NK, Gatalica Z, Watari J, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120:1657–65.
8. Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211–4.
9. Park SH, Lee SS, Choi EK, Kim SY, Yang S-K, Kim JH, et al. Flat colorectal neoplasms: definition, importance, and visualization on CT colonography. AJR Am J Roentgenol 2007;188:953–9.
10. Japanese Society for Cancer of the Colon and Rectum. General rules for clinical and pathological studies on cancer of the colon, rectum, and anus. 7th edition. Tokyo: Kanehara; 2006 (in Japanese).
11. Metz CE, Herman BA, Shen JH. Maximum likelihood estimation of receiver operating (ROC) curves from continuously distributed data. Stat Med 1998;17:1033–53.
12. Fleiss, JL. Statistical methods for rates and proportions. 2nd edition. New York: Wiley; 1981. p. 38–46.
13. Dorfman DD, Berbaum KS, Metz CE. ROC rating analysis: generalization to the population of readers and cases with the jackknife method. Invest Radiol 1992;27:723–31.
14. Fenlon HM, Nunes DP, Schroy PC III, Barish MA, Clarke PD, Ferrucci JT. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. N Engl J Med 1999;341:1496–503.
15. Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. Radiology 2001;219:685–92.
16. Pineau BC, Paskett ED, Chen GJ, Espeland MA, Phillips K, Han JP, et al. Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. Gastroenterology 2003;125:304–10.
17. Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349:2191–200.
18. Nicholson FB, Barro JL, Bartram CI, Dehmeshki J, Halligan S, Taylor S, et al. The role of CT colonography in colorectal cancer screening. Am J Gastroenterol 2005;100:2315–23.
19. Bond JH. Progress in refining virtual colonoscopy for colorectal cancer screening. Gastroenterology 2005;129: 2103–6.
20. Mang T, Peloschek P, Plank C, Maier A, Graser A, Weber M, et al. Effect of computer-aided detection as a second reader in multidetector-row CT colonography. Eur Radiol 2007;17: 2598–607.
21. Halligan S, Altman DG, Mallett S, Taylor SA, Burling D, Roddie M, et al. Computed tomographic colonography: assessment of radiologist performance with and without computer-aided detection. Gastroenterology 2006;131:1690–9.
22. Fidler JL, Johnson CD, MacCarty RL, Welch TJ, Hara AK, Harmsen WS. Detection of flat lesions in the colon with CT colonography. Abdom Imaging 2002;27:292–300.
23. Jensch S, van Gelder RE, Florie J, Thomassen-de Graaf MA, Lobé JV, Bossuyt PM, et al. Performance of radiographers in the evaluation of CT colonographic images. AJR Am J Roentgenol 2007;188:W249–55.
24. European Society of Gastrointestinal and Abdominal Radiology CT Colonography Group Investigators. Effect of directed

training on reader performance for CT colonography: multicenter study. Radiology 2007;242:152–61.
25. Park SH, Ha HK, Kim MJ, Kim KW, Kim AY, Yang DH, et al. False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. Radiology 2005;235:495–502.
26. Kim SH, Lee JM, Lee JG, Kim JH, Lefere PA, Han JK, et al. Computer-aided detection of colonic polyps at CT colonography using a Hessian matrix-based algorithm: preliminary study. AJR Am J Roentgenol 2007;189:41–51.
27. Summers RM, Yao J, Pickhardt PJ, Franaszek M, Bitter I, Brickman D, et al. Computed tomographic virtual colonoscopy computer-aided polyp detection in a screening population. Gastroenterology 2005;129:1832–44.
28. Graser A, Kolligs FT, Mang T, Schaefer C, Geisbüsch S, Reiser MF, et al. Computer-aided detection in CT colonography: initial clinical experience using a prototype system. Eur Radiol 2007;10:2608–15.
29. Dehmeshki J, Halligan S, Taylor SA, Roddie ME, McQuillan J, Honeyfield L, et al. Computer assisted detection software for CT colonography: effect of sphericity filter on performance characteristics for patients with and without fecal tagging. Eur Radiol 2007;17:662–8.
30. Shiraishi J, Abe H, Engelmann R, Doi K. Effect of a high sensitivity in a computerized scheme for detecting extremely subtle solitary pulmonary nodules in chest radiographs: observer performance study. Acad Radiol 2003;10:1302–11.
31. Fenton JJ, Taplin SH, Carney PA, Abraham L, Sickles EA, D'Orsi C, et al. Influence of computer-aided detection on performance of screening mammography. N Engl J Med 2007; 356:1399–409.
32. Taylor SA, Halligan S, Burling D, Morley S, Bassett P, Atkin W, et al. CT colonography: effect of experience and training on reader performance. Eur Radiol 2004;14:1025–33.
33. Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. Stat Med 1998;17:2635–50.
34. Soto JA, Barish MA, Yee J. Reader training in CT colonography: how much is enough? Radiology 2005;237:26–7.
35. Kobayashi T, Xu XW, MacMahon H, Metz CE, Doi K. Effect of a computer-aided diagnosis scheme on radiologists' performance in detection of lung nodules on radiographs. Radiology 1996;199:843–8.
36. Chakraborty DP, Winter LH. Free-response methodology: alternate analysis and a new observer-performance experiment. Radiology 1990;174:873–81.
37. Metz CE. Some practical issues of experimental design and data analysis in radiological ROC studies. Invest Radiol 1989;24:234–45.

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CLINICAL INVESTIGATION

Transcatheter Arterial Chemoembolization (TACE) with Lipiodol to Treat Hepatocellular Carcinoma: Survey Results from the TACE Study Group of Japan

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Abstract The purpose of this study was to retrospectively clarify the current status in Japan of TACE using Lipiodol together with anticancer agents to treat hepatocellular carcinoma (HCC). We retrospectively surveyed 4,659 (average annual total) procedures for HCC over the years 2002–2004 at 17 institutions included in the TACE Study Group of Japan. The survey included six questions that were related mainly to TACE and Lipiodol for HCC treatment. The most frequently applied among the 4,659 procedures at the 17 institutions were TACE (2,310; 50%) and local ablation (1,395; 30%). Five of the institutions applied 201–300 procedures and 4 applied 101–200. Lipiodol was used in "all procedures" and in "90% or more" at seven and nine institutions, respectively. Almost all institutions applied 4–6 (mean, 5) ml of Lipiodol during TACE to treat tumors 5 cm in diameter. In conclusion, this survey clarified that TACE using Lipiodol and anticancer agents is a popular option for HCC treatment in Japan.

Keywords Hepatocellular carcinoma · Transcatheter arterial chemoembolization · Lipiodol · Survey results · Japan

Introduction

The rate of hepatocellular carcinoma (HCC) is increasing and transcatheter arterial chemoembolization (TACE) seems to be becoming more important as a treatment strategy [1, 2]. Although much information about TACE

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for treating HCC has been published [1–36], we consider that to understand the current status of TACE for HCC would be valuable in Japan, where TACE has been applied for more than 20 years [3–22]. We also consider that the concomitant use of iodinated oil (Lipiodol; Lipiodol Ultra-Fluide; Guerbet Co.) for more than 20 years [3–23] should be reviewed [24–26, 32–36]. Although the efficacy of Lipiodol for hepatic TACE has been generally recognized for more than two decades, and segmental or subsegmental TACE using Lipiodol is considered a more effective and less invasive tool for treating localized HCC [9–17], Lipiodol (distributed by Terumo Co. in Japan) has not yet been approved for this application in Japan and other countries. We thus believe that urgent effort is required to obtain official permission from the Pharmaceuticals and Medical Devices Agency (PMDA) of the Japanese Ministry of Health, Labour and Welfare to apply Lipiodol in this manner, based on incontrovertible evidence of expansive usage and value. Therefore, we organized the TACE Study Group in Japan to retrospectively study the issue using a questionnaire at 17 institutions where TACE is frequently applied. We intended to gain fundamental data about TACE and other treatment options for patients with HCC that would reflect the actual use of Lipiodol in clinical practice and its benefits. Our findings should facilitate understanding of the current status of HCC therapy in Japan and establish a foothold for regulatory approval of Lipiodol not only in Japan, but also in other countries.

Materials and Methods

The TACE Study Group distributed questionnaires to 20 institutions throughout Japan and 17 (85%) of them responded regarding 4,774 procedures for HCC including 2,264 TACE (average total per year) during the years 2002–2004. We analyzed the replies to six questions (Q1–Q6) regarding TACE and Lipiodol for the treatment of HCC.

Q1 Annual approximate total of HCC procedures during the years 2002–2004 at the institution.

When 100 procedures were displayed as one average annual frequency unit for convenience in data comparisons, the replies were classified as number of procedures per year per institution as follows: 1, ≤100; 2, 101–200; 3, 201–300; 4, 301–400; 5, 401–500 and 6, ≥501.

Q2 Annual number of individual therapies selected for HCC treatment.

a, Surgery; b, local ablation comprising PEIT (percutaneous ethanol injection therapy), PMCT (percutaneous microwave coagulation therapy), RFA (radiofrequency ablation); c, TACE; d, TACI (transcatheter arterial chemoinfusion therapy); e, CAIC (continuous arterial infusion chemotherapy); f, Cx (systemic chemotherapy); g, RT (radiotherapy).

Q3 Rate of use of Lipiodol in TACE.

Q4 When Lipiodol was not used, reasons why, and methods of TACE.

Q5 Rate of use of Lipiodol in TACI.

Q6 Volume of Lipiodol applied during TACE to treat tumors 5 cm in diameter (clinical stage I).

a, 3–4 ml; b, 4–5 ml; c, 5–6 ml; d, 6–7 ml; e, Other ( ) ml.

Results

Replies (R1–R6) to the questions (Q1–Q6) were as follows.

R1 Four institutions each applied 101–200 and 201–300 procedures per year; three applied ≤100, one applied 401–500 per year, two applied 301–400 per year, and one applied 501 or more per year.

R2 Table 1 reports the annual total of HCC treatments and annual numbers (rate) of the top four individual therapies at 17 institutions. Of the treatments applied at the 17 institutions, the most frequent was TACE (2,264 of 4,774; 47%), followed by local ablation (1,443; 30%), TACI (898; 19%), and resection (341; 9%). The mean annual total of procedures was 281 at 17 institutes. The mean rates of each procedure at these institutions were as follows: TACE, 47%; ablation, 30%; and TACI, 19%.

The total average frequency of TACI in addition to TACE, which treats cancer using a catheter inserted into the hepatic artery, accounted for approximately 66% of the total HCC treatments at 17 institutes.

R3 Regarding Lipiodol in TACE under the premise that Lipiodol is used to prepare a miscible liquid of anticancer drugs (usually Lipiodol emulsion is mixed with anticancer and nonionic contrast agents), seven and nine institutions replied that Lipiodol was used in "all procedures" and in "90% or more," respectively. One institution claimed to

Table 1 Annual total of HCC treatments and annual number (rate) of the top four individual therapies at 17 institutions

Institute	Total therapies/yr	Resections/yr	Ablations/yr	TACE/yr	TACI/yr
Total 17	4,774	391 (8%)	1,443 (30%)	2,264 (47%)	898 (19%)
Mean of 17	281	23 (8%)	85 (30%)	133 (47%)	53 (19%)

Note: TACI, transcatheter arterial chemoinfusion therapy

use "80% or more," but the exact rate was 89%. When the rate of Lipiodol use in TACE at all institutions was calculated simply from all reported TACE over 3 years at 17 institutions, the ratio reached 6,328 of a total of 6,740 TACE (94%) procedures.

R4 Except for the 7 institutions (41%) that used Lipiodol in all TACE procedures, 5 of the 10 institutions that did not use Lipiodol for some TACE procedures replied that Lipiodol might impair hepatic function and 3 replied that they were considering other options. One respondent indicated that TACE did not include Lipiodol at their institution because the therapeutic effect was sometimes limited. Six institutions replied that only gelatin sponge particles are used with anticancer drugs in TACE when Lipiodol is not used.

R5 The rates of Lipiodol use in TACI varied. Although six institutions (35%) used Lipiodol in more than 80% of TACI procedures and four institutions (24%) used it in 40–80%, three institutions (18%) used it in only 20–40 procedures and four institutions (24%) did not use Lipiodol in TACI at all.

R6 The volume of Lipiodol used in TACE to treat tumors 5 cm in diameter in the absence of obviously disrupted liver function (clinical stage I) was 5–6 ml (c) at eight institutions (47%), 6–7 ml (d) at five (29%), 4–5 ml (b) at three (18%), and 3–4 ml (a) at one. The average volume (dose) of Lipiodol applied during TACE for HCC 5 cm in diameter (clinical stage I) essentially reflected the tumor volume as indicated by the diameter (cm) at many of the institutions.

Figure 1 shows an example of a HCC measuring 38 × 45 mm with typical CT patterns that was treated by subsegmental TACE for S5 using 4 ml (6 ml of Lipiodol emulsion) of Lipiodol mixed with 30 mg of doxorubicin (dissolved in 2 ml of nonionic contrast medium and saline) followed by injection with gelatin sponge particles.

Discussion

The rate of HCC is increasing worldwide including in Japan [1, 2]. As HCC frequently presents as multiple lesions, invades surrounding tissues, and is usually accompanied by liver dysfunction, indications for resection or local ablation are restricted even now when earlier stages of HCC are being increasingly diagnosed owing to advances in imaging technology. In addition, multiple lesions frequently recur not only after surgery but also after ablation therapy such as radiofrequency ablation. Therefore, TACE is an important option for HCC treatment and the procedure involves the use of iodized oil (Lipiodol) all over the world.

The efficacy of TACE using Lipiodol for HCC has remained controversial despite evaluations, long-term discussions, and various randomized trials. Whereas some randomized control study findings have questioned the utility of TACE [25–27], more recent reports, also including some randomized studies [24, 30–32], have recognized the value of TACE using Lipiodol [5–23, 33–36]. The most important factors in choosing TACE are to obtain favorable therapeutic effects and to reduce adverse side effects. Thus, the dose of Lipiodol mixed with anticancer drugs should be individually adapted to the tumor size, number of tumors, and hepatic function of each patient. However, the dose of Lipiodol in most randomized control studies was uniform and not adapted to individual needs [25, 26, 31, 33, 36]. We believe that these studies missed the effect of TACE because the doses of Lipiodol and anticancer agents were not optimized, and furthermore, TACE was not repeated before recurrence was diagnosed by imaging, including CT, after the first TACE. However, TACE using Lipiodol is gradually becoming recognized worldwide and randomized control studies seem unnecessary since TACE already seems proven to confer a significant benefit on HCC [2, 24, 30–32].

The present retrospective study clarifies the current status of TACE including the use of Lipiodol for the treatment of HCC at representative institutions that participated in the TACE Study Group in Japan. The results obtained from 17 nationwide institutions showed that although the approximate annual total of HCC procedures over the past 3 years differs at each facility, several hundred HCC procedures per year are performed at the midsize to large leading institutions and >200 treatments are performed annually at more than half of all surveyed institutions. Thus, TACE accounts for 50–60% of all HCC procedures at institutions involved in the TACE Study Group of Japan. Focal radiofrequency ablation therapy is becoming widely prevalent in Japan for localized small HCC lesions. However, TACE has also become a popular strategy for such tumors owing to the use of microcatheters and Lipiodol mixed with anticancer agents, as well as gelatin sponge particles, which are popular for segmental or subsegmental Lipiodol TACE. The excellent effects of segmental or subsegmental Lipiodol TACE in terms of the absence of damage to surrounding normal hepatic tissue have already been proven by histopathological and clinical findings [9–14, 21]. Chemoembolization using Lipiodol combined with percutaneous radiofrequency thermal ablation therapy is becoming another treatment option for HCC, as a larger sphere of ablation can be induced [20]. Repeated TACE with Lipiodol for the recurrence with various collateral pathways is also very useful and important to positively impact the survival of patients with HCC [22]. Therefore, the results of this survey and of most published studies indicate that TACE is an indispensable therapeutic tool that is frequently applied worldwide to treat various types of HCC [2, 4–24, 28–36].

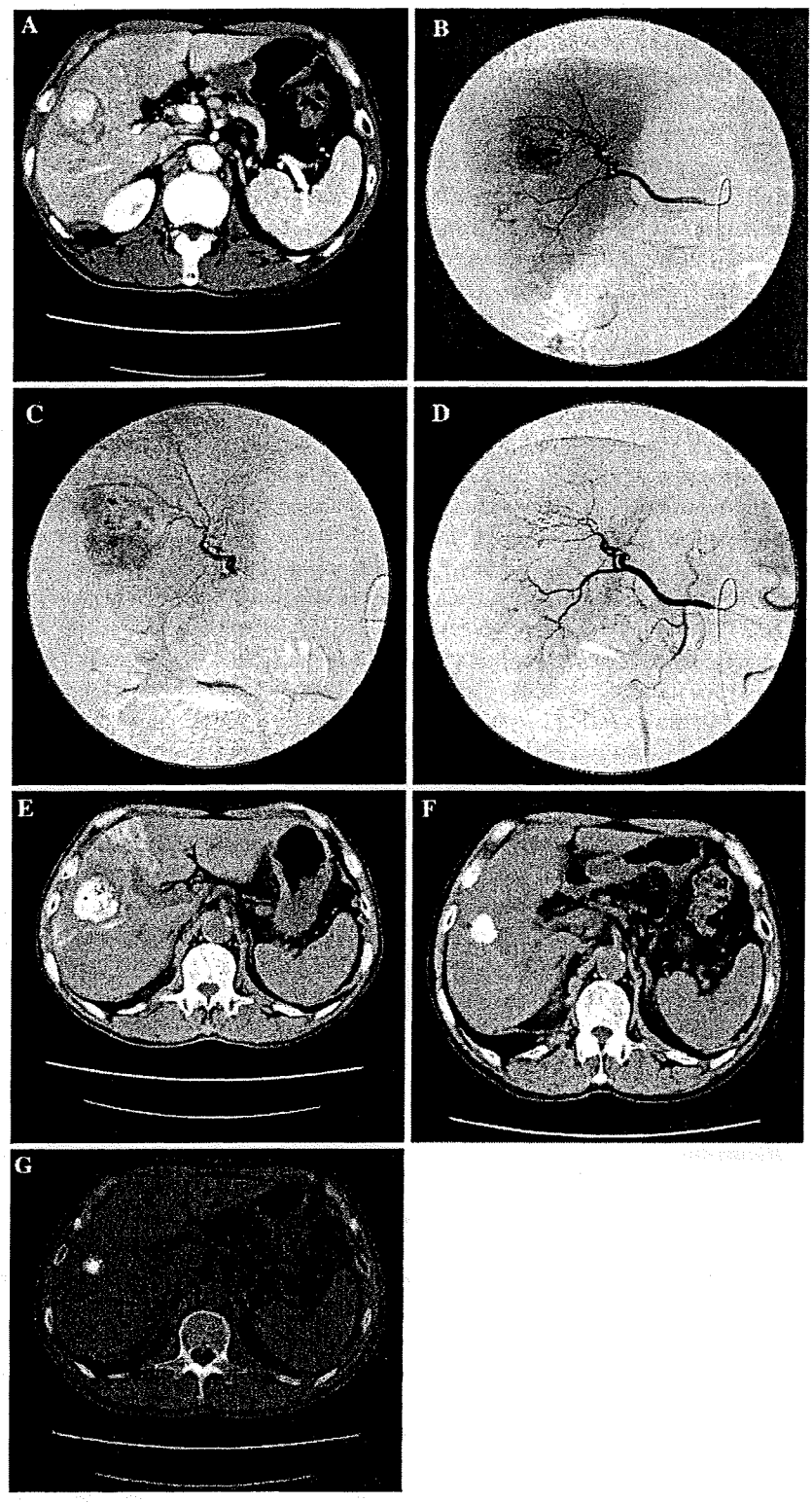

Fig. 1 Hepatocellular carcinoma 38 × 45 mm in diameter showing typical CT profiles and treated with subsegmental TACE using Lipiodol. Subsegmental TACE was performed using 4 ml of Lipiodol (6 ml of Lipiodol emulsion) mixed with 30 mg of doxorubicin in 2 ml of nonionic contrast medium and saline, followed by injection of gelatin sponge particles. (**A**) CT shows hypervascular HCC in S5. (**B**) Hepatic angiogram also demonstrates hypervascular HCC in S5. (**C**) Superselective hepatic angiogram via the anterior-inferior branch (A5) shows hypervascular tumor in S5. (**D**) Hepatic angiogram after subsegmental TACE for S5 shows disappearance of tumor vessels and visualization of surrounding hepatic arteries. (**E**) CT 1 week after subsegmental TACE: Lipiodol is visualized in the embolized S5 area, as well as in the tumor. (**F**) CT 1 year after subsegmental TACE shows homogeneous tumor accumulation of Lipiodol. (**G**) Two years after subsegmental TACE, CT shows dense accumulation of Lipiodol and tumor shrinkage. This tumor did not recur

The efficacy of Lipiodol in TACE for HCC has been recognized by several investigators worldwide [4–24, 28–36], whereas only a few articles indicate contrary findings [25–27]. Although the rate of TACE for HCC differs slightly among institutions, this survey shows that >90% of HCCs treated by TACE included Lipiodol. However, although Lipiodol is generally used as a useful carrier of anticancer agents in Japan and elsewhere, it is not legally permitted for hepatic TACE in Japan. Legal permission to use Lipiodol must be based on clear evidence of expansive usage and value. Therefore, we retrospectively surveyed 17 leading Japanese institutions to generate some fundamental data about the use of hepatic TACE with Lipiodol for treating HCC. Seven institutes used Lipiodol in all TACE procedures, nine used Lipiodol in >90% of them, and one used it in >80%, indicating that Lipiodol/TACE is widely perceived as beneficial.

Under the premise that Lipiodol is used in miscible solutions of anticancer drugs, seven and nine institutions replied that Lipiodol was used in "all" and in "90% or more" of procedures, respectively. One institution replied that Lipiodol was used in "80% or more" of procedures, but the actual frequency was almost 90%.

Although Lipiodol is used in about 40% of all TACE procedures, it is not used at about 60% of institutions in <10% of TACE procedures. This is due to potential impairment of hepatic function among patients with poor liver function or a huge HCC that would require a large volume of Lipiodol. Therefore, TACE is occasionally performed with a reduced amount of Lipiodol mixed with anticancer agents, or a first TACE might use only gelatin sponge particles without Lipiodol and anticancer agents for HCC >10 cm in diameter. A second TACE might include a small volume of Lipiodol mixed with anticancer agent after the tumor has been reduced. When only gelatin sponge particles are used in TACE, some institutions nevertheless essentially agreed that TACE can include Lipiodol mixed with an anticancer agent.

This variable use of Lipiodol in TACI indicates that HCC treatment policies differ among institutions. The total frequency of transcatheter arterial therapy (total of TACE and TACI continuous arterial infusion therapy), which treats cancer using a catheter inserted into the hepatic artery, accounted for 60% of the total HCC procedures. The most frequently applied was TACE, followed by local ablation and TACI. These methods accounted for approximately 90% of all HCC therapies. The average volume of Lipiodol used for TACE for HCCs 5 cm in diameter was almost 5 ml, which reflected the tumor volume and was verified in this survey. Our basic criteria regarding the dose of Lipiodol used for TACE state that that average dose (ml) is roughly equal to the tumor diameter (cm). This is reflected in the tumor volume shown in Fig. 1. We already proposed criteria to select the dose of injected Lipiodol for each patient based on tumor size [9–12, 14, 16]. These criteria have generally been agreed on and are applied in Japan. Therefore, we believe that the survey responses regarding the Lipiodol dose were quite uniform.

A recent article describing the mechanism of action of chemoembolization using Lipiodol in Japan helps to elucidate and support the present study [37].

A prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8,510 patients has been reported [38]. However, the focus of the contents of registration and the questionnaire of that report is completely different from that in the present study.

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References

1. El-Serag HB (2002) Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 35(Suppl):72–78
2. Brown BD, Geschwind JF, Soulen MC, et al. (2006) Society of interventional radiology position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol 17:217–223
3. Kanematsu T, Inokuchi K, Sugimachi K, et al. (1984) Selective effects of lipiodolized antitumor agents. J Surg Oncol 25:218–226
4. Ohishi H, Uchida H, Yoshimura H, et al. (1985) Hepatocellular carcinoma detected by iodized oil. Radiology 154:25–29
5. Sasaki Y, Imaoka S, Kasugai H, et al. (1987) A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. Cancer 60:1194–1203
6. Ohishi H, Yoshimura H, Uchida H, et al. (1989) Transcatheter arterial embolization using iodized oil (Lipiodol) mixed with an anticancer drug for the treatment of hepatocellular carcinoma. Cancer Chemother Pharmacol 23(Suppl):S33–S36
7. Nakamura H, Hashimoto T, Oi H, et al. (1989) Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 170:783–786
8. Konno T (1990) Targeting cancer chemotherapeutic agents by use of lipiodol contrast medium. Cancer 66:1897–1903
9. Uchida H, Ohishi H, Matsuo N, et al. (1990) Transcatheter hepatic segmental arterial embolization using lipiodol mixed with an anticancer drug and gelfoam particle for hepatocellular carcinoma. CardioVasc Interv Radiol 13:140–145
10. Uchida H, Matsuo N, Sakaguchi H, et al. (1993) Segmental embolotherapy for hepatic cancer: key to success. CardioVasc Interv Radiol 16:67–71
11. Uchida H, Matsuo N, Nishimine K, et al. (1993) Transcatheter arterial embolization for hepatoma with Lipiodol. Hepatic arterial and segmental use. Semin Interv Radiol 10:19–26
12. Matsuo N, Uchida H, Nishimine K, et al. (1993) Segmental transcatheter hepatic artery chemoembolization with iodized oil for hepatocellular carcinoma: antitumor effect and influence on normal tissue. J Vasc Interv Radiol 4:543–549

13. Matsui O, Kadoya Y, Yoshikawa J, et al. (1993) Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology 188:79–83
14. Nishimine K, Uchida H, Matsuo N, et al. (1994) Segmental transarterial chemoembolization with Lipiodol mixed with anticancer drugs for nonresectable hepatocellular carcinoma: follow-up CT and therapeutic results. Cancer Chemother Pharmacol 33(Suppl):S60–S68
15. Nakao N, Uchida H, Kamino K, et al. (1994) Determination of the optimum dose level of Lipiodol in transcatheter arterial embolization of primary hepatocellular carcinoma based on retrospective multivariate analysis. CardioVasc Interv Radiol 17:76–80
16. Sakaguchi H, Uchida H, Maeda, et al. (1995) Combined transjugular intrahepatic portosystemic shunt and segmental Lipiodol hepatic artery embolization for the treatment of esophagogastric varices and hepatocellular carcinoma in patients with cirrhosis: preliminary report. CardioVasc Interv Radiol 18:9–15
17. Matsuo N, Uchida H, Sakaguchi H, et al. (1997) Optimal lipiodol volume intracatheter arterial chemoembolotherapy for hepatocellular carcinoma: study based on Lipiodol accumulation pattern and histopathological findings. Semin Oncol 24(Suppl 6):61–70
18. Ueno K, Miyazono N, Inoue H, et al. (2000) transcatheter arterial chemoembolization therapy using iodized oil for patients with unresectable hepatocellular carcinoma: evaluation of three kinds of regimens and analysis of prognostic factors. Cancer 88:574–1581
19. Takayasu K, Muramatsu Y, Maeda T, et al. (2001) Targeted transarterial oily chemoembolization for small foci of hepatocellular carcinoma using a unified helical CT and angiography system: analysis of factors affecting local recurrence and survival rates. AJR 176:681–688
20. Higashihara H, Okazaki M (2002) Transcatheter arterial chemoembolization of hepatocellular carcinoma: a Japanese experience. Hepatogastroenterology 49:72–78
21. Yamakado K, Nakatsuka A, Ohmori S, et al. (2002) Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. J Vasc Interv Radiol 13:1225–1232
22. Iwamoto S, Sanafuji H, Okuda K (2003) Angiographic subsegmentectomy for the treatment of patients with small hepatocellular carcinoma. Cancer 97:1051–1056
23. Miyayama S, Matsui O, Taki K, et al. (2004) Transcatheter arterial chemoembolization for hepatocellular carcinoma fed by the reconstructed inferior phrenic artery: anatomical and technical analysis. J Vasc Interv Radiol 15:815–823
24. Bronowicki JP, Vetter D, Dumas F, et al. (1994) Transcatheter oily chemoembolization for hepatocellular carcinoma: a 4-year study of 127 French patients. Cancer 74:16–24
25. Groupe d'Etude et de Traitment du Carcinome Hepatocellulaire (1995) A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 332:1256–1261
26. Pelletier G, Ducreux M, Gay F, et al. (1998) Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. J Hepatol 27:129–134
27. Bruix J, Llovet JM, Castells A, et al. (1998) Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 27:1578–1583
28. Solomon B, Soulen MC, Baum RA, et al. (1999) Chemoembolization of hepatocellular carcinoma with cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol: prospective evaluation of response and survival in a U.S. population. J. Vasc Interv Radiol 10:793–798
29. Treviasani F, De Notariis S, Rossi C, et al. (2001) Randomized control trials on chemoembolization for hepatocellular carcinoma: Is there room for new studies? J Clin Gastroenterol 32: 383–389
30. Lo CM, Ngan H, Tso WK, et al. (2002) Randomized controlled trial of transarterial Lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164–1171
31. Llovet JM, Real MI, Montana X, et al. (2002) Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma. Lancet 359: 1734–1739
32. Barone M, Ettorre GC, Ladisa R, et al. (2002) Transcatheter arterial chemoembolization (TACE) in treatment of hepatocellular carcinoma. Hepatogastroenterology 50:183–187
33. Chen MS, Li JQ, Zhang YQ, et al. (2002) High-dose iodized oil transcatheter arterial chemoembolization for patients with large hepatocellular carcinoma. World J Gastroenterol 8:74–78
34. Saccheri S, Lovaria A, Sangiovanni A, et al. (2002) Segmental transcatheter arterial chemoembolization treatment in patients with cirrhosis and inoperable hepatocellular carcinoma. J Vasc Interv Radiol 13:995–999
35. Geshwind JF, Ramsely DE, Choti MA, et al. (2003) Chemoembolization of hepatocellular carcinoma: results of a meta-analysis. Am J Clin Oncol 26:344–349
36. Eurvilaichit C (2004) Outcome of transcatheter oily arterial chemoembolization in patients with hepatocellular carcinoma. Hepatogastroenterology 51:20–24
37. Bonneman B (2006) Lipiodol—mechanism of action for chemoembolization. Jpn IVR 21:64–68
38. Takayasu K, Arii S, Ikai I, et al. (2006) Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 131:461–469