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Review Article

The Efficacy of FDG-PET for the Management of Esophageal Cancer: Review Article

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^{18}F-Fluorodeoxyglucose positron emission tomography has become an important informative modality during the past two decades. Because this type of tomography is a functional imaging construct, its primary use is in the field of oncology. It is being used increasingly in the management of several tumor types including esophageal cancer. These tomography scans can distinguish between benign and malignant tumors, identify stages of tumor spread, assess tumor recurrence, and monitor the response of malignant disease to therapy. The aim of this review was to outline the current and future roles of positron emission tomography in the management of esophageal cancer.

Keywords: esophageal cancer, FDG-PET, PET/CT, SUV, staging

Introduction

Esophageal cancer has proven to be one of the most difficult malignancies to cure despite improved surgical techniques, reduced perioperative mortality, and the introduction of multimodality therapy.[1,2] Accurate tumor staging—particularly with regard to the depth of tumor invasion, involvement of lymph nodes, and distant metastasis—is essential for optimal treatment selection and delivery. It facilitates individually tailored patient management.[1] Preoperative chemotherapy and chemoradiotherapy have been introduced as therapeutic options for locally advanced cancer to downsize the primary tumor. This step increases the rate of complete resection, which improves local tumor control and prevents the formation of distant metastases.[3,4]

Perioperative mortality and morbidity are frequent in esophageal cancer patients. Thus, the use of neoadjuvant therapy is important as some patients have tumors that show a good response to it and may even be cured without undergoing surgery. It is, therefore, important to establish a method that can distinguish patients who will have a partial response from those who will have a complete response to neoadjuvant therapy.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), a noninvasive imaging modality, has been widely investigated during the past two decades in regard to its use in the management of esophageal cancer.[5–15] This imaging technique may facilitate definitive diagnoses in patients with malignant disease by differentiating between benign and malignant tumors, assessing extension of the disease, detecting tumor recurrence, and monitoring the response to therapy.[16–18]

In this article, we review the role and usefulness of FDG-PET for disease staging and treatment of esophageal cancer.

Imaging with PET or PET/CT

Accurately staging esophageal carcinoma is of paramount importance. The prognosis and the treatment modalities and their sequences are highly variable, depending on the disease stage. FDG-PET is a promising modality for such accurate staging. FDG is the most common radiopharmaceutical used for PET imaging. It differentiates physiologically active tissues from malignant tumors based on enhanced glucose transport in the tumors. FDG

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(an analog of glucose) and glucose are taken up by cells via glucose transporters (GLUTs), which are located in cell membranes. The tendency of malignant cells to express abundant GLUT-1[19,20] is the key to the amount of uptake. An abundance of these transporters may be a good predictor of the malignant potential of these cells and may correlate with the invasive potential of a tumor and the poor survival rates associated with esophageal cancer.[21]

In the early days of FDG-PET application,[7,22–24] fusion imaging using PET and computed tomography (CT) was nonexistent. PET/CT is a relatively new imaging modality that can detect functional abnormalities. It is better than PET alone because the location of the FDG uptake is revealed by CT.[25] Using this co-registration, motion artifacts are minimized, and the incidence of misregistration problems and diagnostic confusion is significantly decreased. The data acquired from PET images are reconstructed using standard reconstruction algorithms, which incorporate ordered subset expectation maximization. The data thus obtained may be analyzed quantitatively, semi quantitatively, or qualitatively. The most commonly used parameter for FDG uptake quantification is the standardized uptake value (SUV), which is the ratio of the injected radioactivity to total body weight.

Staging of Esophageal Cancer

1. Primary lesion

Endoscopy, endoscopic ultrasonography, esophagography, CT, and/or magnetic resonance imaging (MRI) have been used to determine the depth of tumor invasion. Recently, magnifying endoscopy has been used to determine tumor depth, as well.[26,27] It is difficult to judge the depth of invasion of esophageal cancer using FDG-PET.[10,28,29]

Kato et al. reported the detection rate of primary tumor for each depth of invasion (T1–T4).[10] According to that report, the primary tumor was visualized by FDG-PET in 119 of 149 patients (80%). FDG uptake was detected in 21 of 49 patients with T1 tumors (43%), 9 of 10 patients with T2 tumors (90%), 50 of 51 patients with T3 tumors (98%), and 39 of 39 patients with T4 tumors (100%). Among the 81 patients who initially underwent surgery, FDG uptake was detected in 17 of the 40 who had pT1 tumors (43%), in 3 of 17 (18%) patients with pT1a tumors (remaining within the muscularis mucosae), and in 14 of 23 (61%) patients with pT1b tumors (involving the submucosa). FDG uptake rates in patients with pT2, pT3, and pT4 tumors were 83%, 97%, and 100%, respectively. Based on these results, it cannot be clearly stated that FDG-PET is useful for detecting early esophageal cancer. Himeno et al. reported that pathological mucosal cancers were not detected by FDG-PET, whereas tumors that had invaded more deeply than the submucosal layer were detectable in all cases. Therefore, they stated that FDG-PET is useful for deciding if there was an indication for endoscopic resection.[30] In our recent study, the detection rate of mucosal cancer was poor, whereas submucosal (or deeper) cancers were detected in all cases (**Fig. 1**). At present, FDG-PET does not effectively determine tumor depth. It can be used, though, for tumor localization of advanced cancer.

2. Lymph node metastasis

Establishing the presence (or absence) of lymph node metastasis in patients with esophageal cancer is important because it affects the choice of treatment. A high frequency of lymph node metastasis is characteristic of esophageal cancer. Even when the tumor depth is at the submucosal level, lymph node metastasis is present in about 40% of patients.[31] The presence of lymph node metastasis, the extent of the metastatic field, and the number of metastatic lymph nodes influence the prognosis. Morphological imaging (e.g., by CT) evaluates the metastasis according to its size, morphology, and enhanced status, among other parameters. Morphological imaging cannot distinguish nonspecific lymph node swelling from metastatic swelling.

FDG-PET is able to diagnose a metastatic lymph node regardless of its size. Kato et al. reported that the minimum size of metastatic lesions that FDG-PET can detect is 6 mm diameter.[10] Thus, FDG-PET cannot detect micrometastases. There have been some reports of FDG accumulating in the presence of inflammatory lymphadenopathy. False-positive uptake by hilar lymph nodes is often observed, so diagnoses must be carefully constructed.[11]

Kato et al. reported that FDG-PET showed 77.8% sensitivity, 92.9% specificity, and 84.4% accuracy. They also showed that CT scanning had 61.1% sensitivity, 71.4% specificity, and 65.6% accuracy.[10] A meta-analysis that summed up the 12 reports concerning FDG-PET[12] found that the sensitivity, specificity, positive predictive value, and negative predictive value were 51%, 84%, 81%, and 57%, respectively. Other reports have demonstrated the superior performance of FDG-PET compared to CT.[10,32]

Flamen et al. compared FDG-PET to endoscopic ultrasonography (EUS) in regard to diagnosing locoregional

Table 1 Diagnostic accuracy of lymph node metastasis of esophageal cancer per lymph nodal group

	Lymphnodegroupaccuracy				
	Sensitivity	Specificity	Accuracy	PPV	NPV
CT (n = 117)	26.5 (45/170)	97.5 (1722/1766)	91.3 (1767/1936)	50.1 (45/89)	93.2 (1722/1847)
PET (n = 117)	32.9 (56/170)	98.9[b] (1747/1766)	93.1[a] (1803/1936)	74.7[b] (56/75)	93.9 (1747/1861)
PET/CT (n = 50)	46.0[b,d] (40/87)	99.4[c] (986/992)	95.1[c,d] (1026/1079)	87.0[c] (40/46)	95.5[a] (986/1033)

PPV: positivepredictivevalue; NPV: negativepredictivevalue
[a]P <0.05vs.CT; [b]P <0.01 vs.CT; [c]P <0.001 vs. CT and [d]P <0.05 vs.PET

lymph node metastasis. They found that the sensitivity of PET was 33%, and that of EUS was 81%; in contrast, the specificity of PET was 89%, and that of EUS was 67%. Concerning the diagnosis of regional lymph nodes and distant metastatic lymph nodes, the sensitivities of PET and CT + EUS were 43% and 48%, respectively (not significant), whereas the specificities were 98% and 90%, respectively (significant).[33] Based on these studies, the sensitivity of FDG-PET is not high for diagnosing lymph node metastasis, but the specificity is desirable. The differential diagnosis of metastatic lymph nodes versus inflammatory swelling lymph nodes is important for diminishing the false-positive and false-negative rates. Dual-time-point FDG-PET, which utilizes the difference in the maximum FDG uptake time by inflammation tissue versus cancer tissue, is a promising modality for solving this problem.[34]

By adding FDG-PET to usual modalities such as CT and EUS, it is possible to improve diagnostic precision. Kato et al. proved that the diagnostic precision of FDG-PET for diagnosing lymph node metastases is superior to that of CT (**Table 1**).[35]

3. Distant metastasis

Distant metastasis is the most important factor that restricts therapeutic strategies. Distant metastases of esophageal cancer have been frequently observed in liver, lung, and bone, among other sites. FDG-PET is thought to be the most important modality in the diagnostic armamentarium for detecting distant metastatic disease in patients with esophageal cancer. In earlier studies, PET has revealed occult distant metastases at nodal and nonnodal sites in 5%–40% of patients[36–38] with moderate sensitivity (~67%) and high specificity (~97%).[12] It may also reveal osseous metastases that were not detected by conventional bone scintigraphy.[39] It has been reported that PET is superior to bone scintigraphy for detecting osteolytic lesions but not for osteoblastic lesions.[40] Using a logistic regression model in patients examined preoperatively with CT, EUS, and/or PET, one investigation found that PET was the only modality that predicted resection with curative intent because it excluded the presence of distant metastases. Those authors concluded that PET may be used to prevent unnecessary surgical exploration in patients who have M1 disease.[41] In another study, the use of FDG-PET changed the clinical management of 27 of 68 patients (40%). In 12 patients, therapy was changed from curative to palliative (owing to detection of previously unsuspected distant metastases); in 3 patients, it was changed from palliative to curative; and in 12 patients, there was a change in the treatment modality or delivery but not in the treatment intent.[42]

Distant metastasis is an important factor when determining if there is an indication for surgical therapy. FDG-PET, which can search for lesions in the entire body with high specificity, is an essential modality.

Diagnosis of Recurrent Disease

The recurrence rate following radical therapy for esophageal cancer is high. Therefore, close follow-up is required. The usual imaging modalities (i.e., CT and MRI) often have some difficulty detecting a recurrent lesion because they detect abnormal lesions based on normal anatomy. FDG-PET is an extremely useful modality for detecting not only a locoregional recurrence but a distant metastatic recurrence (**Fig. 2**).[13,43] Kato et al. reported that the sensitivity, specificity, and accuracy of PET for diagnosing recurrence in locoregional lymph nodes were 100%, 75%, and 84%, respectively. The corresponding figures for CT were 84%, 86%, and 85%. These authors also reported that the sensitivity of PET is better than that of CT, but the specificity of CT is better than that of PET in regard to detecting distant organ re-

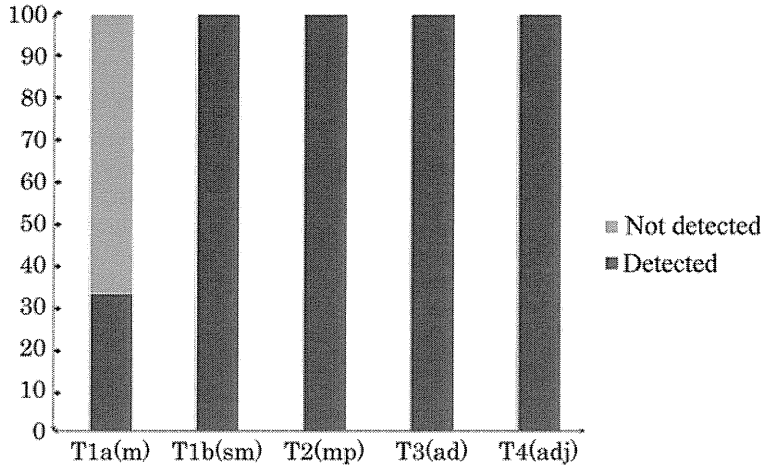

Fig. 1 primary esophageal cancer detection rates at each depth of invasion.
The detection rate of tumors invading the mucosal layer (T1a) was 33% and was 100% for tumors that invaded more deeply than the submucosal layer (T1b).

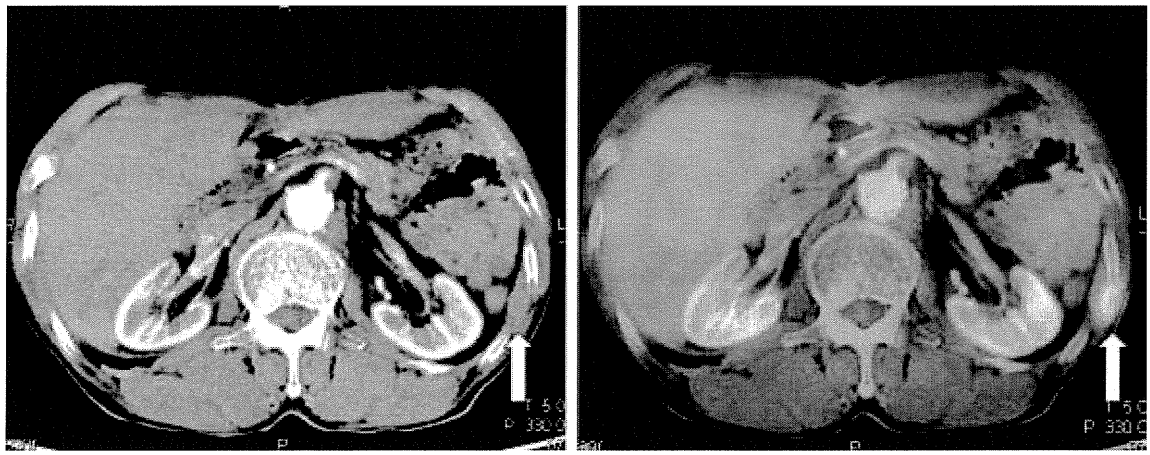

Fig. 2 Patient whose recurrent lesion was detected by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). A | B
He had undergone esophagectomy with lymphadenectomy 11 months before, and a thoracic wall recurrence was detected by FDG-PET. **A**: Computed tomography (CT) scan. It is difficult to identify the recurrent lesion (arrow). **B**: PET scan. A recurrent lesion is obvious at the left thoracic wall (arrow). Maximum standard uptake value (SUVmax) was 6.3.

currence.[13] The low specificity of PET was derived from false-positive FDG uptake in the reconstructed gastric tube, anastomosis, and hilar lymph nodes. It is improved by acquiring anatomical information using PET/CT.

Evaluation of the Response of CRT

For advanced esophageal cancer, neoadjuvant chemotherapy or chemoradiotherapy (CRT) is performed as a strategy to downstage (downsize) malignant lesions.[44–50] Among digestive malignancies, esophageal cancer is a promising candidate for a cure by CRT.[51,52] In some patients, the result of definitive CRT is equal to that achieved with a radical operation.[53] Patients whose tumors show a good response to neoadjuvant therapy may be cured without undergoing surgery.[54] Therefore, it is important to establish a method that can predict responders.

FDG-PET is useful for evaluating the response to CRT. CT and MRI cannot distinguish viable tumor tissues from fibrotic or necrotic residual tissues, whereas

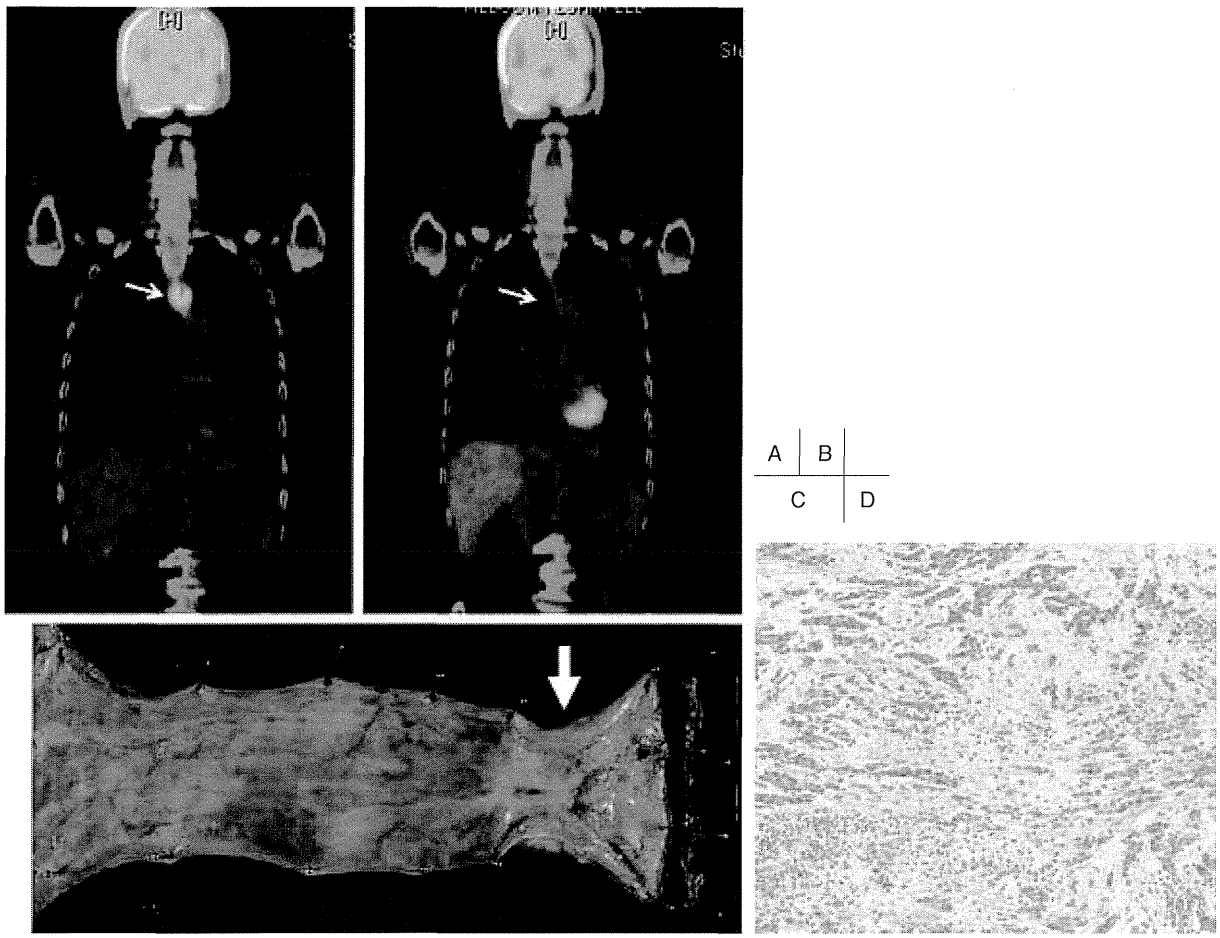

Fig. 3 PET scan of a patient rated as having a pathological partial response.
The scan was used as a monitor for neoadjuvant chemotherapy. **A**: The esophageal cancer demonstrated significant FDG uptake (arrow) (SUVmax 12.36) before neoadjuvant chemotherapy. **B**: Three weeks following chemotherapy, the FDG uptake was significantly decreased (arrow) (SUVmax 3.22). **C**: Subtotal esophagectomy was performed 4 weeks after finishing chemotherapy. The exposed tumor showed reduction (arrow). **D**: Pathology examination revealed a partial response (grade 1).

PET can perform a functional evaluation on the basis of metabolic information (**Fig. 3**).[17] The efficacy of FDG-PET as a predictor of patients' responses to CRT has been reported in regard to esophageal cancer.[18,55] These studies discussed the effectiveness of PET evaluation by the rate at which the SUV was reduced. Pathological or clinical responders may be distinguished from nonresponders by establishing an optimal reduction rate. One study of adenocarcinoma of the esophagogastric junction noted that the change in FDG uptake 14 days after chemotherapy was significantly related to the rate at which the tumor volume was reduced.[56] There is some doubt about measuring the efficacy of CRT using a decrease in the SUV reduction rate. The SUV of FDG-PET reflects glucose metabolism. Therefore, reduction rates may be a good index of the pathological response but not the number of apoptotic cells. To begin to evaluate the number of residual viable tumor cells, the maximum SUV should be determined. Some studies have certified the importance of the FDG uptake value after induction or preoperative therapy.[57,58] Others have noted that the baseline SUV can predict the response to CRT.[59,60]

Regardless of those findings, FDG-PET is a key modality for predicting the response and pathological efficacy of chemotherapy and CRT. We believe that in the near future FDG-PET will be active in predicting the response to molecular targeting therapy and immunotherapy.

Summary

FDG-PET is being increasingly used for diagnosing esophageal cancer and its initial staging. Its use in detecting

recurrence during follow-up and monitoring the response to treatment is now standard practice. PET provides information that is complementary to that obtained by CT. The most important application of PET may be the selection of potential responders for various treatment modalities. Its survival benefit during multidisciplinary therapy for esophageal cancer is limited to those who display a pathological response.[61-66] Pathological responses can be seen only when the patient undergoes surgery, but FDG-PET has the potential to predict an exact pathological response after induction therapy. That is, second-line therapy may be chosen based on FDG-PET results. The precision of FDG-PET and PET/CT needs improvement. Larger studies may better clarify whether there is indeed an incremental diagnostic improvement with FDG-PET.

In conclusion, FDG-PET is an important diagnostic modality in the therapeutic strategy for esophageal cancer. If higher-precision FDG-PET can be developed, it will contribute to improving the survival statistics for esophageal cancer patients. Also, with the identification of new FDG-PET tracers, we expect further expansion of the application of PET imaging in the field of esophageal cancer.

Disclosure Statement

Masanobu Nakajima and other co-authors have no conflict of interest.

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Adult Intussusception Caused by Descending Colon Cancer during Chemotherapy of Stomach Cancer Recurrence

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Key Words
Intussusception · Descending colon cancer · Stomach cancer recurrence · Chemotherapy

Abstract
Intussusception in adults is uncommon, and it is rare in the descending colon because of its fixation to the retroperitoneum. We herein describe a case of intussusception caused by descending colon cancer. A 74-year-old man was admitted to our hospital for treatment of vomiting and abdominal pain. He had undergone chemotherapy for lymph node recurrence of stomach cancer for about 4 years. Computed tomography revealed a 'target mass' with a tumor in the descending colon. We diagnosed his illness as intussusception of a descending colon tumor and performed emergency laparotomy. Conservative resection was performed following anastomosis after reduction of the intussusception. The tumor was pathologically diagnosed as poorly differentiated adenocarcinoma with neuroendocrine features. To the best of our knowledge, this is the first report of an intussusception caused by descending colon cancer incidentally diagnosed during chemotherapy for stomach cancer recurrence.

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Introduction

Intussusception is most commonly encountered in infants and children, although approximately 5% of cases occur in adults. In fact, it accounts for an estimated 1% of all cases of bowel obstruction in adults. Adult intussusception of the colon is rare and often originates from neoplasia [1]. This condition generally does not present with any specific symptoms. The diagnosis can be in emergency situations, with the aid of integrated examinations. The association of readily available diagnostic means, such as radiological and ultrasonographic studies, may yield reliable findings [2, 3]. These help in formulating a diagnosis of the nature and site of occlusion. However, this condition is often subsequently confirmed intraoperatively. Preoperative diagnosis of this condition can be difficult in emergency cases.

We herein describe a case of adult intussusception of the descending colon caused by a malignant tumor. Intussusception of the descending colon generally does not readily occur because the descending colon is anatomically fixed to the retroperitoneum [4]. Moreover, this patient had undergone chemotherapy for lymph node recurrence of stomach cancer for about 4 years, which could not prevent colon cancer. The progression of this patient's condition seemed to indirectly suggest a difference in biological malignancy between stomach cancer and colon cancer.

Case Report

A 74-year-old Japanese man was admitted to our hospital for treatment of vomiting and abdominal pain on June 15, 2011. Physical examination revealed a temperature of 36.9°C, blood pressure of 175/105 mm Hg and a pulse rate of 65 beats/min. His abdominal pain continued intermittently for approximately 12 h in the night. Clinical examination revealed a distended abdomen with provocative pain in the left upper quadrant and a palpable, fist-sized mass. Blood tests showed a slightly elevated C-reactive protein level of 1.15 mg/dl, although other tests, including tumor markers, were within normal limits.

The patient had a past history of distal gastrectomy for stomach cancer in December 2003 and was visiting our hospital for chemotherapy for lymph node recurrence around the aorta approved since March 2007. This patient underwent 12 courses of irinotecan (100 mg/m^2 weekly for 3 weeks followed by 2 weeks of rest) followed by 14 courses of S-1 (80 mg/m^2 weekly for 4 weeks followed by 2 weeks of rest) and 5 courses of paclitaxel (100 mg/m^2 weekly for 3 weeks followed by 1 week of rest). Computed tomography (CT) indicated that the lymph node recurrence had disappeared on June 1, 2011, resulting in a complete response.

At his visit to our hospital, CT revealed a 'target mass' in the descending colon, suggesting the existence of a tumor in the head of the intussusception (fig. 1), whereas colonoscopic examination had revealed normal results in June 2008. We diagnosed his illness as intussusception of a colon tumor and performed emergency laparotomy. At surgery, the descending colon was intussuscepted into itself by the tumor. The intussusceptum was easily isolated because the fixation between the descending colon and the retroperitoneum was relatively weak. Reduction of the intussusception was performed before the resection following anastomosis because of the shortness and tension in the neighboring colon. The left colon, including the ischemic area and tumor, and regional lymph nodes were removed. An end-to-end anastomosis was primarily fashioned between the transverse colon and sigmoid colon. The postoperative course was uneventful, and the patient was discharged 14 days after surgery.

Macroscopically, the surgical specimen contained a 5.3 × 3.5 cm protuberant tumor at the proximal edge of the 16-cm-long ischemic area in the descending colon (fig. 2). Microscopic examination revealed poorly differentiated adenocarcinoma with invasion into the subserosa and ischemic wall on the anal side of the tumor by hematoxylin-eosin staining (fig. 3a). The regional

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lymph nodes did not have metastasis. The tumor was partially positive for chromogranin A, KIT, and CD56 by immunohistological staining, resulting in an adenocarcinoma with neuroendocrine features (fig. 3b–d).

Discussion

Most colon intussusceptions in adults are caused by malignant tumors, although other causes and idiopathic forms of intussusception have been reported [1–3]. These intussusceptions are frequently located in the flexible portions of the colon, for example the sigmoid colon or cecum [5, 6]. Intussusception of the descending colon is rarer because the descending colon is anatomically fixed to the retroperitoneum [4]. Incomplete fixation between the retroperitoneum and descending colon might result in the presently described condition.

Few general surgeons encounter more than one or two patients with colon intussusception during their careers, and most cases are undiagnosed before surgery. Previous papers reported that CT is the most accurate imaging modality for diagnosing intussusception [1, 2]. The characteristic CT findings of intussusception include an early target mass with enveloped, eccentrically located areas of low density [7].

Reduction of intussusceptions with suspected malignancy is not generally advisable because it may cause bowel perforation and tumor cell dissemination [8]. However, reduction may be advisable to accurately determine the range of resection for minimally invasive surgery [6]. In our case, conservative resection was performed following anastomosis after reduction of the intussusception. If the intussusception had been operatively reduced, it would have been difficult to anastomose primarily because of the shortness and tension in the neighboring colon.

It was thought that colon cancer in this case occurred during the past 3 years, because colonoscopic examination had revealed a normal study in 2008. On the other hand, our patient had received several kinds of chemotherapy for lymph node recurrence of stomach cancer for about 4 years and had obtained a complete response. Thus chemotherapy seems to be generally effective for both gastric cancer and colon cancer, but could not prevent colon adenocarcinoma in our case. One reason could be the mixture of neuroendocrine features, because neuroendocrine carcinomas often show resistance to chemotherapy [9].

Colon intussusception in adults is generally rare. To the best of our knowledge, this is the first report of an intussusception caused by descending colon cancer incidentally diagnosed during chemotherapy for stomach cancer recurrence. The progression of this patient's condition also suggested a difference in the biological malignancy between stomach cancer and colon cancer.

Disclosure Statement

The authors have no conflicts of interest.

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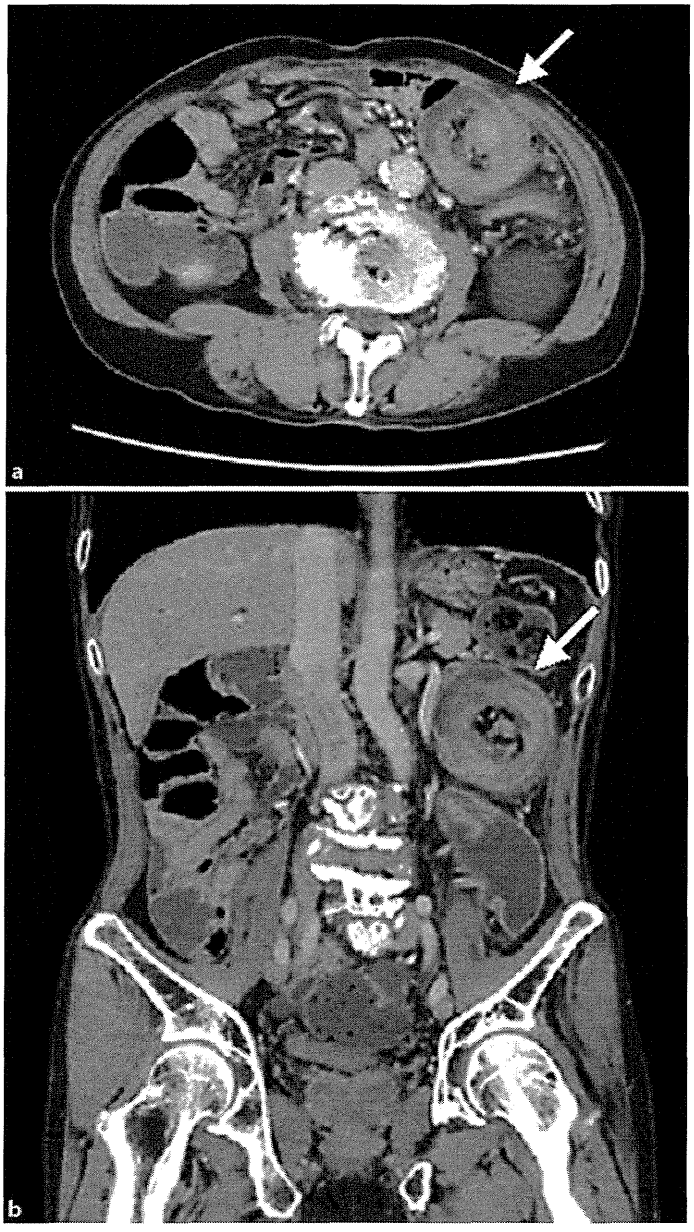

Fig. 1. Abdominal CT indicated enlargement of the descending colon wall within the intussusception (arrows), suggesting the existence of a tumor in the head. **a** Transverse slice. **b** Sagittal slice.

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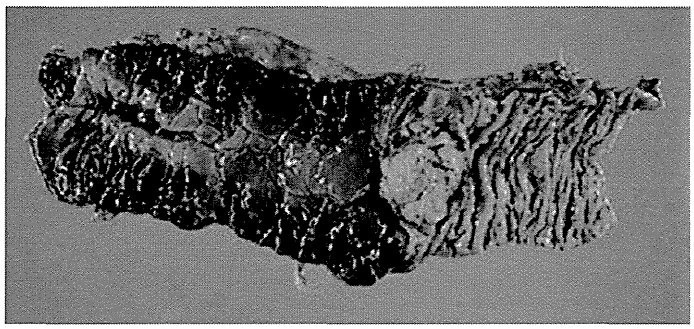

Fig. 2. The surgical specimen contained a 5.3 × 3.5 cm protuberant tumor that was thought to be the lead point of the intussusception. The ischemic area of the wall was 16 cm along the anal side of the tumor.

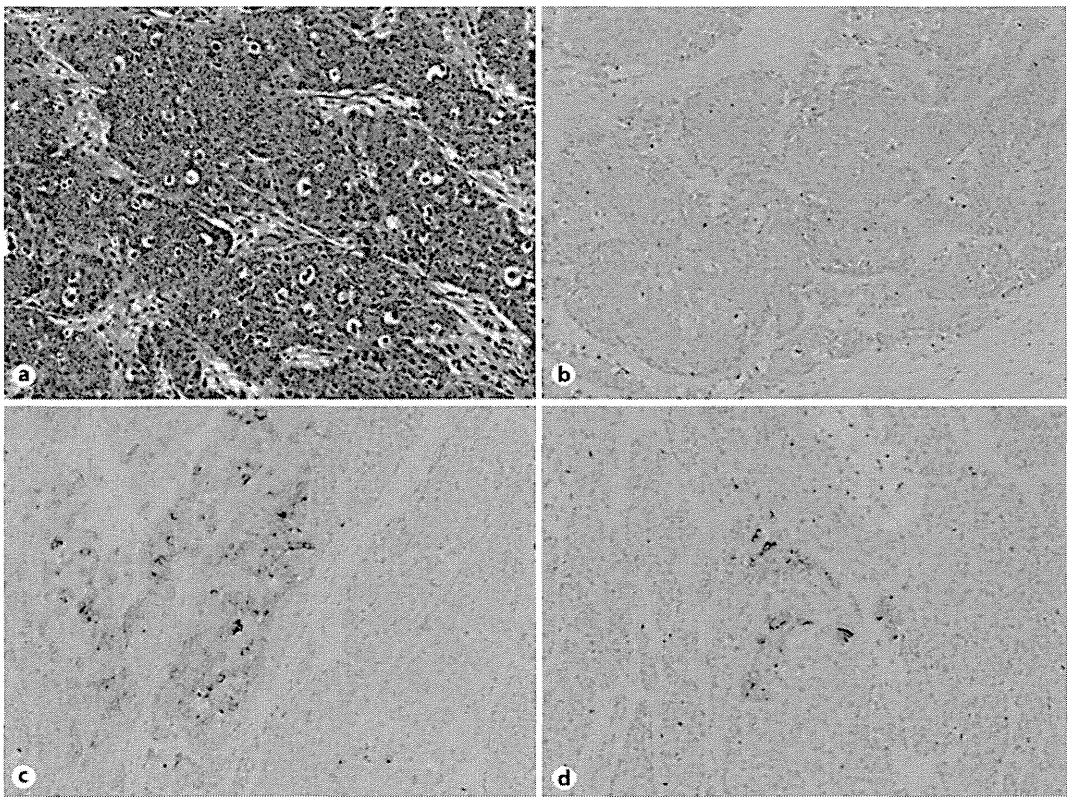

Fig. 3. Microscopic examination. **a** The tumor was a poorly differentiated adenocarcinoma with invasion into the subserosa (hematoxylin-eosin staining, ×100). **b–d** The tumor was partially positive for chromogranin A, KIT, and CD56 by immunohistological staining (×100).

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A Case of Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis Successfully Treated by a Combination of Intra-Arterial Infusion 5-Fluorouracil, Cisplatin, and Systemic Interferon-α Therapies

Tsutomu Kobayashi[1], Hideki Suzuki[1], Norio Kubo[1], Akira Watanabe[1], Shigeru Sasaki[1], Wataru Wada[1], Kenichiro Araki[1], Tatsuo Shimura[2], Hiroyuki Kuwano[1]

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Case Report

A Case of Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis Successfully Treated by a Combination of Intra-Arterial Infusion 5-Fluorouracil, Cisplatin, and Systemic Interferon-α Therapies

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A 58-year-old female with hepatitis C was referred to our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. After thorough examination, tumor thrombosis was detected on the main trunk of the portal vein, and we decided to administer a combination of subcutaneous interferon-alfa and intra-arterial 5-fluorouracil. However, after 2 cycles of treatment, this regimen was ineffective, and thus cisplatin (CDDP) was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography. Hence, chemotherapy was considered effective and stopped. Two years after chemotherapy, Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II) levels were within normal limits. Combination therapies have been recognized recently, and judging from the above case, the addition of CDDP to the combination regimen can prove beneficial.

Key words: Hepatocellular carcinoma – Portal vein tumor thrombosis – INF-α – Intra-arterial chemotherapy

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There is no effective treatment for cases of hepatocellular carcinoma (HCC) with main portal vein tumor thrombosis (PVTT). Moreover, the prognosis of inoperable cases is extremely poor, and some authors have reported that the average life span after diagnosis is 3 to 6 months. Recently, however, a combination of systemic interferon-alfa (INF-α) and intra-arterial 5-fluorouracil (FU) has been reported to improve the prognosis of the disease. Furthermore, partial and complete response cases are reported to achieve high survival rates of 100% at 1 year and 80% at 3 years. The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis and is therefore being considered a standard treatment option for HCC with PVTT. If the treatment is not effective, the patient can be administered additional medication. In this case study, it was seen that systemic INF-α therapy and intra-arterial infusion of 5-FU in combination with cisplatin (CDDP) were effective for both recovery and long-term survival of a patient with HCC and PVTT.

Case report

A 58-year-old female was referred to the outpatient clinic of our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. The patient was infected with hepatitis C virus (HCV) by blood transfusion 35 years ago, but she did not receive treatment and visited our hospital for a thorough examination and treatment. Clinical tests on admission indicated abnormal liver function, and laboratory data showed abnormally high levels of aspirate aminotransferase (AST; 166 IU/L) and alanine aminotransferase (ALT; 188 IU/L). The levels of total bilirubin were normal (0.8 mg/dL). The prothrombin time was 82%, and the indocyanine green retention rate at 15 minutes was 36.8%. The levels of tumor markers AFP and PIVKA were found to be elevated at 48.2 ng/mL and 19,362 U/mL, respectively, indicating advanced HCC. Liver cirrhosis was defined as grade A according to Child's classification. CT and abdominal angiography revealed PVTT, which was then treated by INF-α and intra-arterial 5-FU combination chemotherapy. Hepatectomy and embolization therapy were contraindicated in this case. Pretreatment images are shown in Fig. 1. CT arterial portography and CT hepatic arteriography revealed that the tumor was in the right lobe of her liver and had infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium revealed a flow defect at the main trunk of the portal vein. ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed abnormal uptake in the right lobe of her liver (maximum standardized uptake value, 3.0; Fig. 1). The protocol of this combination therapy was as follows: 5-FU 500 mg/d (days 1–7, weeks 1–2), INF-α 5 million units (days 1, 3, and 5; weeks 1–4). However, after 2 cycles of treatment, this regimen was ineffective, thus CDDP was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET (Fig. 2). Hence, chemotherapy was considered effective and stopped. A combination therapy of INF-α and revabirin was started to combat hepatitis C. Two years after chemotherapy, AFP and PIVKA-II levels were within normal limits. However, 3 years and 6 months after chemotherapy, a new lesion was detected in the left lobe of the liver on CT scan, along with increased HCV titers; and the lesion was treated by radiofrequency ablation (RFA). New lesions were detected in the right lobe of the liver after 1 year and after 2 years of RFA treatment, and were treated by transcatheter arterial embolization (TAE) therapy. After treatment with TAE, no lesion was detected, and the patient achieved a 5-year survival. Changes in tumor marker levels and HCV titers are shown in Fig. 3.

Discussion

The incidence of HCC, one of the most common cancers, has been on the rise in Japan for the past 30 years.[1] Recent developments in imaging techniques have made it possible to detect even a small lesion at an early stage. Although prognosis of total HCC has improved, that of advanced cases with PVTT continues to be poor. Numerous therapies have been implemented to treat advanced cases with PVTT, but none have been effective. The prognosis of inoperable cases that have been reported is estimated to be extremely poor, with an average life span of only 3 to 6 months after diagnosis.[2,3] Recently, a combination of intra-arterial 5-FU and systemic INF-α was reported to be more effective than treatment with arterial 5-FU alone for inoperable cases, resulting in an improved prognosis compared with operable cases.[4–6] Obi reported that the complete response cases of HCC with PVTT, which constitute 15%, showed a 1-year survival rate of over 80%.[4] The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis.[7,8] Prognosis of high-expression

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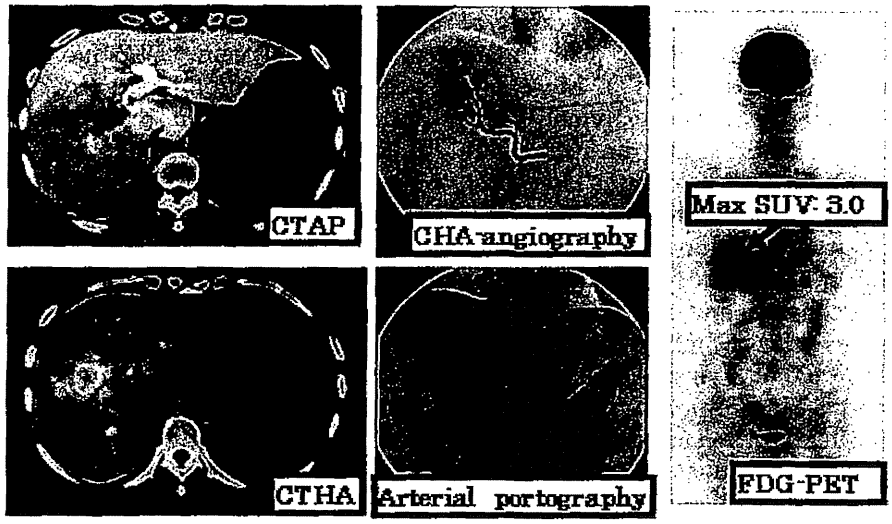

Fig. 1 CT arterial portography and CT hepatic arteriography reveal a tumor, in the right lobe of the liver, that infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium reveals a flow defect at the main trunk of the portal vein. FDG-PET reveals abnormal uptake in the right lobe of the liver (maximum standardized uptake value, 3.0).

groups of type-I interferon receptor is reported to be better than that of low-expression groups for gastrointestinal cancer; however, the function of this receptor in HCC has not been identified.[7,8] In our case, the above-mentioned combination therapy was only slightly effective and complete response was achieved with the addition of CDDP. Addition of other chemotherapy drugs is considered to be effective in cases that do not respond to standard combination therapy. The recent developments in radiation techniques have enabled the use of local radiation therapy. Radiation-induced hepatitis usually occurs after whole liver irradiation to total 30 Gy; however, three-dimensional conformal radiation therapy (3DCRT) for PVTT has been reported to be effective, even with high focal doses (60 Gy), without causing any damage to the normal liver parenchyma tissue.[9–11] Some studies conducted on TAE and 3DCRT have reported significantly high survival rates in the responders compared with the nonresponders, while others have reported no difference in survival rates between the 2 groups.[10,11] The drawback of this TAE-3DCRT combination therapy was that the therapy failed to suppress intrahepatic metastasis.[10] Large-scale studies of 3DCRT and arterial chemotherapy have not yet been conducted, thus making the findings of our study on combination therapy valuable. We experienced one case of HCC with PVTT that showed complete recovery with local radiation therapy for PVTT and intra-arterial 5-FU infusion. The patient is currently alive having survived for

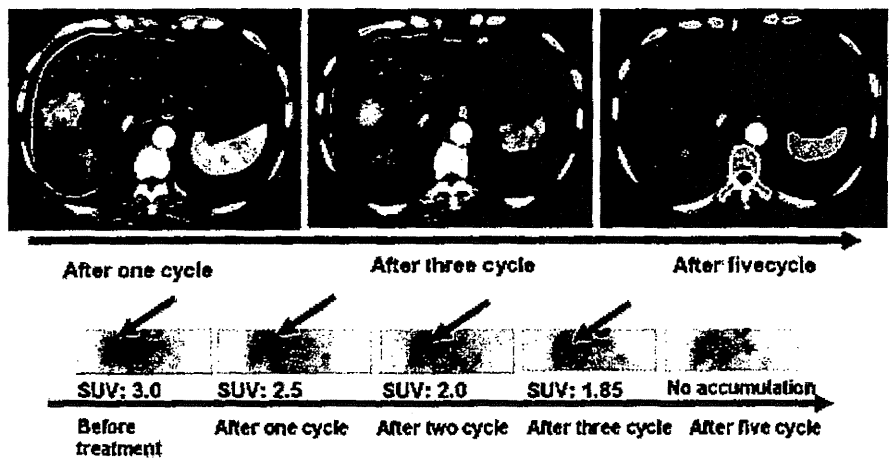

Fig. 2 On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET.

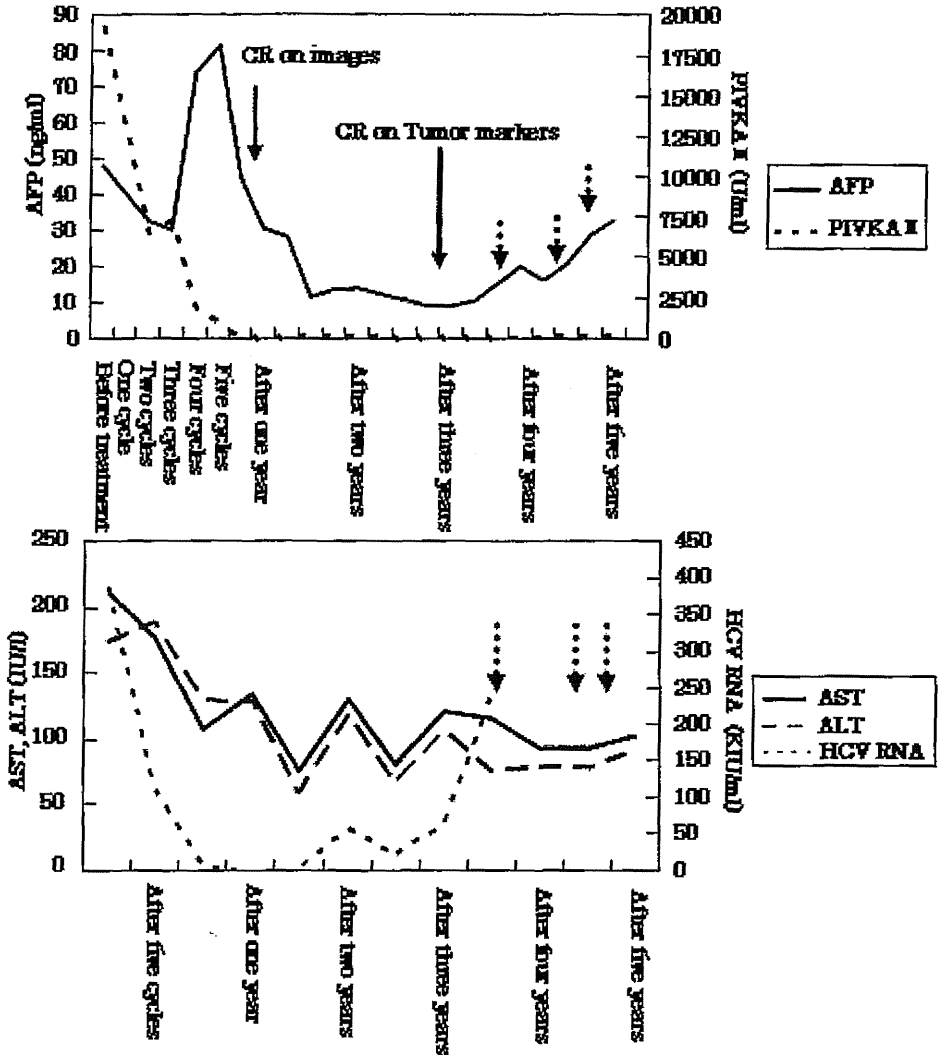

Fig. 3 The top graph shows changes in tumor markers. The bottom graph shows AST, ALT and HCV titers. The broken arrow indicates a period of recurrence.

over 5 years without recurrence. We might include local radiation in the treatment regimen for similar/future cases. In the future, a combination of local radiation therapy along with INF-α, intra-arterial 5-FU, and other carcinostatic drugs should be considered as the basic protocol for HCC with PVTT.

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