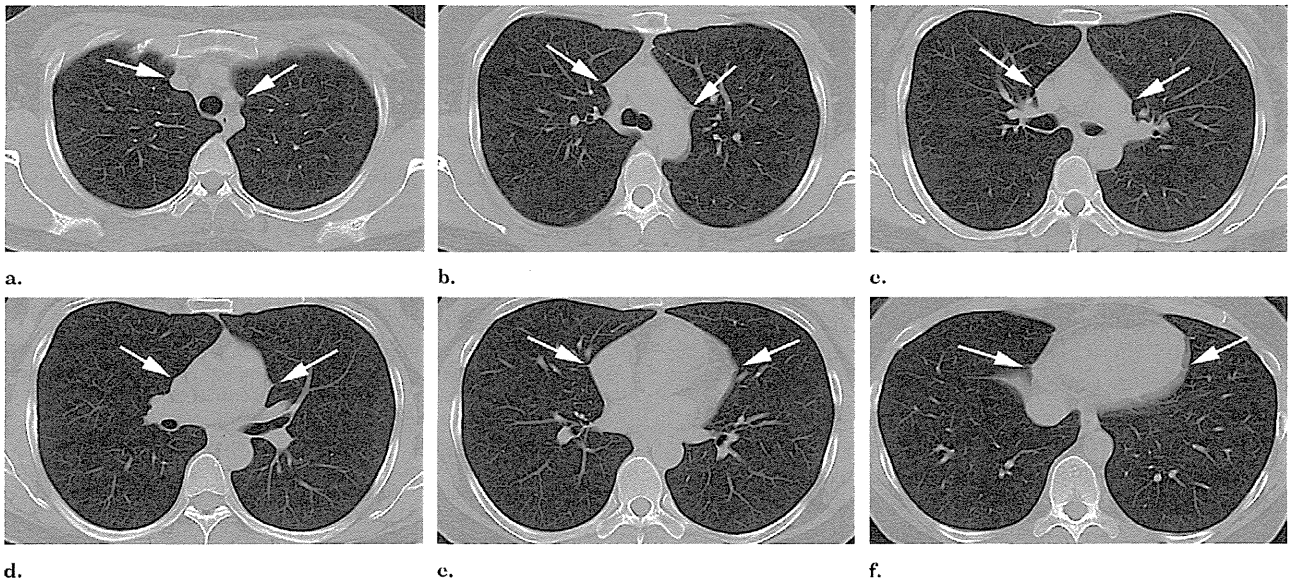

Figure 2. Chest CT images from a 41-year-old woman. Arrows denote the location of the phrenic nerves on each slice. **(a, b)** The right phrenic nerve lies lateral to the right brachiocephalic vein and the superior vena cava. The left phrenic nerve runs along the lateral aspect of the transverse arch of the aorta. **(c, d)** The two nerves subsequently pass anterior to their respective pulmonary hila. **(e, f)** The two nerves traverse inferiorly in a broad vertical plane along the margin of the heart between the fibrous pericardium and the mediastinal pleura.

phrenic nerve injury are asymptomatic, as revealed in the present study. Ablation operators should consider the anatomy of the phrenic nerve to minimize the risk of this complication. The anatomy of the phrenic nerve on CT images is shown in Figure 2. The phrenic nerves lie along the lateral mediastinum and run from the thoracic inlet to the diaphragm. They run through the upper chest, medial to the mediastinal pleura and the apex of the right or left lung. The right phrenic nerve lies lateral to the right brachiocephalic vein and the superior vena cava. The left phrenic nerve runs along the lateral aspect of the transverse arch of the aorta. The two nerves subsequently pass anterior to their respective pulmonary hila and traverse inferiorly in a broad vertical plane along the margin of the heart between the fibrous pericardium and the mediastinal pleura (5).

A previous study (10) showed impaired pulmonary function following unilateral diaphragmatic paralysis caused by iatrogenic complications, tumors, trauma, infection, and unknown causes. The present study also showed significant decreases in pulmonary function in cases of phrenic nerve injury after RF ablation; phrenic nerve injury reduced the values of VC and FEV1.0 by approximately 20%. The decrease in pulmonary function after RF ablation was quite a bit higher than that in a previous study (11) on influence of RF ablation of lung tumors on pulmonary function (mean proportions of VC and FEV1.0 after RF ablation of 93% and 95% at 1 mo and 95% and 95% at 3 mo, respectively).

Multivariate analysis was performed by using values of tumor size and proximity of the phrenic nerve to the tumor. Although the maximum power and electrode size were found to be significantly associated with phrenic nerve injury by univariate analysis, those variables were not evaluated in the multivariate analysis. We selected the electrode size according to the tumor size, and we varied the RF power according to the electrode size. Therefore, electrode size and maximum power were substantially correlated with tumor size. To avoid multilinearity, those two variables were excluded from the multivariate analysis. The multivariate analysis demonstrated that only the proximity of the phrenic nerve to the tumor was a significant independent risk factor.

We demonstrated that nine of the 10 cases of phrenic nerve injury (90%) were accompanied by procedural pain in the shoulder, teeth, or mandible. Such pain is likely referred from phrenic nerve stimulation. In addition to their function of providing motor innervation to the diaphragm, phrenic nerves transmit sensory information from the central intrathoracic and peritoneal surfaces of the diaphragm, radiating painful sensations from these areas to the neck and shoulder. Left shoulder pain caused by splenic rupture, or Kehr sign, is a typical example of referred pain from the phrenic nerve (12). Referred pain of the teeth and mandible may be explained by interconnections between the nuclei of the phrenic nerve and the trigeminal nerve, which carries sensations from these areas (13). Our results indicate that referred pain during RF ablation procedures may be predictive of the development of phrenic nerve injury after the procedure.

The creation of an artificial pneumothorax may offer a prophylactic treatment for phrenic nerve injury. Thornton et al (3) reported a single case in which phrenic nerve injury was avoided by creating an artificial pneumothorax between the tumor and the phrenic nerve. Similarly, creation of an artificial pneumothorax may protect the mediastinum and chest wall (14). In addition, an artificial pneumothorax is useful in minimizing pain during ablation by separating

ablated tumors from the chest wall and parietal pleura (15). However, this technique would not be feasible in the presence of pleural adhesions (14). Conversely, the use of thoracoscopic guidance instead of the traditional percutaneous approach would enable direct visualization and guarantee separation of the tumor from the mediastinal structures.

There are several limitations to the present study. This is a retrospectively designed study. The development of phrenic nerve injury was not evaluated by using a nerve conduction study. Although we reviewed postprocedural chest radiographs that were obtained 3 hours after RF ablation and on the following day, we did not review subsequent chest radiographs because they were not routinely obtained thereafter at determined time points. Therefore, delayed development of phrenic nerve injury was not evaluated in this study. Pulmonary function data were missing in four of the 10 cases of phrenic nerve injury. The phrenic nerve is not usually clearly visible on CT images, so, in the majority of cases, it was necessary to predict the location of the phrenic nerve based on standard anatomy; consequently, the estimated distance between a tumor and the phrenic nerve may be inaccurate.

In conclusion, the incidence of phrenic nerve injury after RF ablation of lung tumors was 1.3%. Phrenic nerve injury caused a significant decrease in pulmonary function. The proximity of the phrenic nerve to the tumor was an independent risk factor for phrenic nerve injury.

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INTRODUCTION TO REVIEW ARTICLES

Current status of interventional oncology

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One of the recent advances in the field of cancer treatment is the appearance of interventional oncology. Interventional oncology now seems to be the fourth pillar of cancer care following surgical, radiation, and medical oncology. Modern advances in imaging and image guidance for the detection of cancer have led to the minimally invasive image-guided treatment of cancer, which is called interventional oncology. Interventional oncology can cause less morbidity than open surgery, and less toxicity than chemotherapy and radiation.

Interventional oncology itself is a new concept–combining interventional radiology with oncology. Interventional radiology is a medical sub-specialty of radiology which utilizes minimally invasive image-guided procedures to diagnose and treat diseases in nearly every organ system. The concept behind interventional radiology is to diagnose and treat patients using the least invasive techniques currently available in order to minimize risk to the patient and improve health outcomes.

The origins of interventional radiology are in the angiographic Seldinger techniques developed by cardiovascular radiologists in the late 1950s and early 1960s. Using these angiographic techniques, one can gain access to many organ systems by percutaneous puncture. The performance the radiologic procedures employed in interventional radiology has been facilitated by the development of high-resolution fluoroscopy, ultrasound, computed tomography (CT), and magnetic resonance imaging. Moreover, interventional radiology has benefited from growing developments in materials science, information technology, and biotechnology. Interventional radiology can be used to treat various diseases, including vascular, biliary, urological, neurological, and gastrointestinal diseases. Interventional radiology uses various techniques such as vascular embolization, vascular dilatation and recanalization, stent placement, vascular infusion, drainage tube placement, needle biopsy, foreign body retrieval, and thermal ablation.

Cancers in various organs can be now treated by using these interventional techniques, and the number of cancer patients treated by interventional techniques is rapidly increasing worldwide. For example, many patients with hepatocellular carcinoma have transcatheter arterial chemoembolization and/or radiofrequency ablation now. If the tumor size is not so large, renal cell carcinoma can be completely cured by image-guided radiofrequency or cryoablation. In the present decade, patients with stage 1 lung cancer have been cured by CT-guided radiofrequency ablation or by the use of microwave energy. Thus, the field of interventional radiology in cancer treatment has been enlarged. As a result, the concept of interventional oncology has emerged, which means that an independent category has appeared in interventional radiology.

In interventional oncology, physicians need to be skilled not only in the use of interventional techniques and in the diagnostic interpretation of images but to also have knowledge of oncology and patient care. To improve the level of evidence of the efficacy of interventional therapy in cancer, well-designed prospective clinical studies should be performed. The development of materials and devices for interventional oncology continues to contribute to improvements in the prognosis of cancer patients. Interventional therapy combined with chemotherapy and/or radiotherapy may be one of the new strategies for cancer treatment.

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In this issue of the *International Journal of Clinical Oncology*, Drs. Arai and Osuga, who are representative interventional oncologists in Japan, report topics of interest in interventional oncology that reveal the utility and significance of its existence.

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Review Article

Lung Radiofrequency Ablation: Potential as a Therapy to Oligometastasis and Oligo-Recurrence

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The early results (e.g., patient survival) of RFA for the treatment of patients with NSCLC and pulmonary metastasis from various primary lesions including colorectal cancer, lung cancer, hepatocellular carcinoma, renal cell carcinoma, and sarcoma appear encouraging and suggest the potential to offer long-term survival for the patients with oligo-recurrence or oligometastasis of lung cancer. The usefulness of RFA for oligo-recurrence or oligometastasis of lung cancer should be clarified by prospective studies in the future.

1. Introduction

Primary lung cancer is the most common malignancy and the leading cause of death from cancer worldwide. In addition, the lungs are the second most frequent site of metastasis from extrathoracic cancers and the only site of metastasis in 20% of such cases. Surgical resection is the first-line treatment for nonsmall-cell lung cancers (NSCLC) and offers the best treatment opportunity. Surgery is also accepted as a treatment option for carefully selected patients with metastatic lung cancer. However, surgical resection is not suitable for many patients mainly because of the advanced stage of cancer, compromised lung function, and/or comorbidities. Although chemotherapy, radiation therapy, or a combination of these serves as alternative treatments for such patients, complete remission of the disease is rarely achieved. Therefore, research that focused on alternative therapies for lung cancer has been extensive in the past decades; such therapies include stereotactic radiation therapy, cryoablation, laser ablation, and radiofrequency (RFA).

RFA causes focal coagulation necrosis of tissue by delivery of energy in the form of an alternating electrical current with a frequency of 460 to 500 kHz in the range of radio waves. The location of the ablative effect is determined by the precise placement of the radiofrequency electrode, usually using imaging guidance. The radiofrequency electrical current is concentrated near the noninsulated tip of the electrode, and the circuit is completed by returning either to electrical grounding pads usually located on the patient's thighs. The alternating electrical current causes ionic dipolar molecules in surrounding tissue and fluids to agitate, resulting in frictional heating that is greatest adjacent to the noninsulated portion of the electrode. The heat energy is then distributed radially to surrounding tissues. When radiofrequency current is applied in a slow, controlled fashion, the tissue heating is local, typically ellipsoid in shape, and predictable in distribution.

At first, RFA was noted as a therapy for hepatocellular carcinoma. The favorable outcomes of the RFA in the liver have encouraged the application of this technique to cancer in other organs. In 2000, Dupuy et al. [1] firstly reported clinical application of this technique in the lung. Since then, RFA has been gaining popularity rapidly as a treatment of lung cancer. RFA of lung cancer is usually performed under CT-guidance and the techniques are quite simple and similar to those used for CT-guided lung biopsy. Herein, we review clinical outcomes of RFA of lung cancer and discuss the potential to be used as a therapy to oligometastasis and oligo-recurrence.

2. Rationale for RFA of Oligometastasis and Oligo-Recurrence

Oligometastasis and oligo-recurrence, proposed by Niibe and Hayakawa [2], are the condition of one or a few metastatic or recurrent lesions without and with controlled primary tumor, respectively. Although significance of local therapy of metastatic lesions for survival benefit may be controversial, the International Registry of Lung Metastases (IRLM) [3] reported that 5-year overall survival for patients with complete resection of metastatic lung tumors was 36%, compared with 13% for patients without it. Further, for the patient for whom lung metastases were completely resected, survival depended on tumor number; that is, smaller number of metastases indicated better survival. Such data may suggest the rationale for applying local therapy including RFA for oligometastasis and oligo-recurrence. The registry also reported that the patients with disease-free intervals of 36 months or more had better prognosis. Thus, the patients with slow growing tumors are more appropriate candidates for RFA.

3. RFA of Primary Lung Cancer

There have been several studies on RFA in the management of primary lung cancers. In 2007, Simon et al. [4] reviewed 75 cases of previously untreated stage I NSCLC, resulting in overall survival of 78%, 57%, and 27% at 1, 2, and 5 years, respectively. Those results seemed to compare favorably with previous studies using external beam radiotherapy in similar stage tumors. Survival was significantly associated with tumor size, with approximately 50% of 5-year survival for the patients with tumors <3 cm. Further encouraging results were reported in a prospective multicenter study by Lencioni and coworkers [5]. Their study included 33 patients with NSCLC treated with RFA; of those, 13 patients had medically inoperable stage I NSCLC. The overall survival in patients with NSCLC was 70% and 48% at 1 and 2 years, respectively, with cancer-specific survival of 92% and 73% at 1 and 2 years. Subgroup analysis revealed 2-year overall survival of 75% and 2-year cancer-specific survival of 92% in patients with inoperable stage I NSCLC. Hiraki et al. [6] reported the outcomes of 27 patients with stage I NSCLC who were treated with RFA. During median follow-up period of 22 months, the mean survival time was 42 months. The overall survival and cancer-specific survival rates were 90% and 100% at 1 year, 84% and 93% at 2 years, and 74% and 83% at 3 years, respectively. Most recently, Hiraki et al. [7] have updated their data using 50 patients with stage I NSCLC. During median follow-up period of 37 months, a median survival time was 67 months, the overall, cancer-specific and disease-free survivals were 94%, 100%, and 82% at 1 year, 86%, 93%, and 64% at 2 years, and 74%, 80%, and 53% at 3 years, respectively. Despite favorable survival data, local progression was observed in 16 (31%) of the 52 tumors. Lanuti et al. [8] reported that during a median follow-up of 17 months, median survival time was 30 months for 31 patients; survaial rate was 85% at 1 year, 78% at 2 years, and 47% at 3 years; local progression rate was 32%. Pennathur et al. [9] reported that during a mean follow-up of 29 months, survival rate for 19 patients was 95% at 1 year, and 68% at 2 years; local progression rate was 42%.

With regard to oligo-recurrence of NSCLC, Kodama et al. [10] carried out an interesting study. Their study included 44 patients who underwent lung RFA for recurrent NSCLC after surgery. Forty-three patients had no extrapulmonary metastasis; one patient had liver and splenic metastasis, which was also treated with RFA. Single or multiple intrapulmonary recurrences were ablated. During mean follow-up period of 29 months, the overall survival rates were 98% at 1 year, 73% at 2 years, and 56% at 3 years. The recurrence-free survival rates were 77% at 1 year and 41% at 3 years. Tumor size and sex were independent significant predictors in the multivariate analysis. This study indicated that RFA may offer a chance of long-term survival for the patients with oligo-recurrence of primary lung cancer.

4. RFA of Metastatic Lung Cancer

4.1. Metastasis from Colorectal Cancer. The cancer that most frequently metastasizes to the lung is colorectal cancer. Approximately 10% of the patients who undergo curative resection for colorectal cancer develop lung metastases [11]. Standard treatment options include surgical resection and chemotherapy. Many surgeons believe that surgical resection is the best treatment that offers the potential for long-term survival in selected patients. Several large studies on pulmonary metastasectomy have demonstrated similar survival after surgery, with approximately 40% of the 5-year survival rate. Further, systematic review of 1684 patients by Pfannschmidt et al. [12] showed 48% of 5-year survival. However, patients with pulmonary metastases are often nonsurgical candidates because of other coexistent metastases, poor cardiopulmonary function, or refusal to undergo surgery. A recent chemotherapy regimen using fluorouracil and leucovorin with irinotecan or oxaliplatin has been shown to prolong survival, but the long-term results are still less than satisfactory, with a median survival of 14.8–21.5 months for the patients with metastatic colorectal cancer [13].

The prospective multicenter study by Lencioni et al. [5] showed that overall survival rate was 89% at 1 year and 66% at 2 years in patients with colorectal metastases; cancer-specific survival was 91% at 1 year and 68% at 2 years. Hiraki et al. [14] also assessed survival rates for 27 patients with pulmonary metastases from colorectal cancer. During the median follow-up period of 20.1 months after RFA, the overall survival rates were 96% at 1 year, 54% at 2 years, and 48% at 3 years. The most significant prognostic factor was the presence of extrapulmonary metastasis at the time of RFA. While patients with extrapulmonary metastasis never survived for 2 years, survival rates for patients without extrapulmonary metastasis were favorable, indicating 100% at 1 year, 76% at 2 years, and 68% at 3 years. These results showed the potential of long-term survival of the patients with oligo-recurrence from colorectal cancer with RFA. Yamakado et al. [15] reported the outcomes of a retrospective multicenter study on RFA for pulmonary metastases from colorectal cancer. The estimated 3-year survival rate was

46% for all patients. Extrapulmonary metastasis, tumor size, and the carcinoembryonic antigen level were significant prognostic factors in the univariate analysis. The first two factors were significantly independent prognostic factors in the multivariate analysis. Thirty-six patients with small lung metastases (< or =3 cm) and no extrapulmonary metastases had a 3-year survival rate of 78%. Yamakado et al. [16] also reported single center experiences of RFA for pulmonary metastases from colorectal cancer. For 78 patients, the 1-, 3-, and 5-year survival rates were 84%, 56%, and 35%, respectively, during a mean follow-up period of 25 months. The median survival time was 38.0 months. Univariate analysis revealed maximum tumor diameter of 3 cm or less, single-lung metastasis, lack of extrapulmonary metastasis, and normal carcinoembryonic antigen (CEA) level as better prognostic factors. The latter two were significant independent prognostic factors. The 1-, 3-, and 5-year survival rates were 97.7% (95% CI, 93.3–100%), 82.5% (95% CI, 68.2–96.8%), and 57.0% (95% CI, 34.7–79.2%) in 54 patients with no extrapulmonary metastases and 96.9% (95% CI, 90.8–100%), 86.1% (95% CI, 71.1–100%), and 62.5% (95% CI, 36.3–88.6%) in 33 patients with negative CEA levels. More recently, Chua et al. [17] reported promising long-term outcome obtained by a prospective trial of 108 patients with pulmonary metastases from colorectal cancer. The median survival reached 60 months, which appeared equivalent to data obtained by metastasectomy.

4.2. Metastasis from Hepatocellular Carcinoma. Hiraki et al. [18] performed a retrospective multicenter study on RFA for pulmonary metastases from hepatocellular carcinoma HCC. This study included 32 patients who had no intrahepatic recurrence or had treatable intrahepatic recurrence, who had no other metastases, and for whom RFA was performed with curative intent (i.e., not palliatively). The overall survival rates were 87% at 1 year and 57% at 2 and 3 years during a median follow-up period of 20.5 months. Median and mean survival times were 37.7 months and 43.2 months, respectively. Significantly better survival rates were obtained for patients with an absence of viable intrahepatic recurrence, Child-Pugh grade A, absence of liver cirrhosis, absence of hepatic C virus infection, and α-fetoprotein level of 10 ng/mL or lower at the time of RFA. These results seem to suggest that pulmonary metastasis from HCC is suitable candidates for RFA, if primary cancer is well controlled (i.e., oligo-recurrence).

4.3. Metastasis from Renal Cell Carcinoma. In cases of pulmonary metastases from renal cell carcinoma, patient survival was evaluated using data from 2 institutions [19]. This study included 39 nonsurgical candidates who were divided into 2 groups: a curative ablation group, which was formed by 15 patients with 6 or fewer lung metastases measuring ≤6 cm that were confined to the lung and who had all lung tumors ablated, and the palliative ablation group, which included 24 patients with extrapulmonary lesions, 7 or more lung tumors, or large tumors of >6 cm, and who had mass reduction. The overall survival rates in the curative and palliative ablation groups were 100% and 90% at 1 year, 100% and 52% at 3 years, and 100% and 52% at 5 years, respectively. The maximum lung tumor diameter was a significant prognostic factor.

4.4. Metastasis from Sarcoma. Palussière et al. [20] reported the outcomes of RFA for pulmonary metastases from various kinds of sarcoma. This study included 29 patients with a maximum of 5 lung metastases and without extrapulmonary metastasis (i.e., oligo-recurrence). During median follow-up period of 50 months, the 1- and 3-year survival rates were 92.2% and 65.2%, respectively. Median disease-free survival was 7 months. This study suggests that RFA may offer a chance for long-term survival for patients with oligo-recurrence from sarcoma, although the disease may recur in a relatively short-term followup.

Nakamura et al. [21] reported on RFA for 20 patients with pulmonary metastases from musculoskeletal sarcomas. During the mean follow-up period of 18 months (range, 7 months to 54 months), 9 of 20 patients died of lung tumor progression. The 1- and 3-year survival rates from RF ablation were 58% and 29% with a median survival time of 12.9 months in all patients. Survival rate for 14 patients with controlled primary tumor (33% at year) was not significantly different from that for 6 patients without controlled primary tumor (52% at 1 year). Survival rate for 10 patients with ≤5 lung metastases (38% at year) was not significantly different from that for 10 patients with >5 lung metastases (88% at 1 year). Thus, survival did not seem to depend on whether oligo-recurrence or not in the population that they studied.

5. Advantages and Limitations of RFA

Major limitation of RFA may be limited local efficacy. RFA induces various complications. Food and Drug Administration in the United States made a public announcement regarding deaths following RFA of lung tumors in 2007. Rare but serious complications may occur including bronchopleural fistula [22], pulmonary artery pseudoaneurysm [23], systemic air embolism [24], injury of the brachial nerve and the phrenic nerve [25, 26], pneumonia [27], and needle-tract seeding of cancer [28]. A case of fatal acute deterioration of interstitial pneumonia after RFA has been also reported [29]. Survey is required to recognize an incidence of acute deterioration after RFA in the patients with interstitial pneumonia and thereby to determine a role of RFA in such patients.

Notable advantages of RFA include limited influence on pulmonary function. According to a report by Ambrogi et al. [30], the mean forced vital capacity (VC) was 2.63 and 2.80 L at 1 and 3 months, respectively, compared with 2.91 L before RFA; the mean forced expiratory volume in 1 s (FEV(1)) was 1.71 and 1.86 L at 1 and 3 months, respectively, compared with 1.97 L before RFA. The multicenter prospective study by Lencioni et al. [5] also showed mean forced VC and FEV1 of 2.6 and 1.7 L, respectively, at 1 month, compared with 2.9 and 1.9 L, respectively, before RFA in 22 patients with non-small cell lung cancer. Tada et al. [31] reported that the mean VC and FEV(1) before RFA and 1 and 3 months after RFA were 3.04 and 2.24 L, 2.79 and 2.11 L, and 2.85 and 2.13 L,

respectively. De Baère et al. [32] reported that pulmonary function did not decrease after RFA; the mean VC and FEV1 were 2.9 and 2.2 L, respectively, after RFA, compared with 2.9 and 2.2 L, respectively, before RFA.

The freedom to perform the procedure regardless of any previous therapy is another important advantage. Adhesion after pulmonary surgery or radiation-induced pneumonitis is not an obstacle for performing the procedure. Thus, the procedure may be used as a salvage treatment for oligo-recurrence after surgery and radiation therapy. At the same time, RFA procedure is not an obstacle for performing concurrent or adjuvant chemotherapy or adjuvant radiation therapy. According to the Norton-Simon hypothesis [33], the effectiveness of chemotherapy agents is proportional to the growth rate of the tumor and the fastest tumor growth rates occur when tumors are not bulky. Therefore, if RFA can downsize the primary tumor, the remaining tumor cells may become more sensitive to chemotherapy. The combination with such therapeutic modalities is expected to increase the efficacy of RFA not only through an additive effect but also due to synergistic effects [34]. The availability to repeat procedures whenever required is also an important advantage. Although RFA results in relatively high rate of local failure, local failure may be salvaged by repetition of the procedure [35].

6. Conclusions

In conclusion, the early results of RFA for the treatment of patients with NSCLC and pulmonary metastasis from various primary cancers appear encouraging and suggest the potential to offer long-term survival for the patients with oligo-recurrence or oligometastasis of lung cancer. The usefulness of RFA for oligo-recurrence or oligometastasis of lung cancer should be clarified by prospective studies in the future.

Abbreviation

RFA: Radiofrequency ablation.

Conflict of Interests

The authors have no conflict of interests.

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ORIGINAL ARTICLE

Observer variation study of the assessment and diagnosis of incidental colonic FDG uptake

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Abstract
Purpose The aim of this study was to evaluate the interpretations of incidental colonic 18F-FDG uptake made by 10 experienced readers and to more clearly identify the pattern of suspicious colonic FDG uptake. The potential contributions of delayed FDG-PET scanning and of immune fecal occult blood testing (FOBT) in making a diagnosis were also analyzed.
Materials and methods Visual interpretations by 10 readers were made for 147 FDG uptake sites from 126 PET scans (cancer, 38 sites; adenoma, 43 sites; and no abnormality, 66 sites) with colonic FDG uptake. Assessments for the early FDG-PET images were (1) FDG uptake pattern, (2) FDG uptake degree, and (3) likelihood of malignancy. For the delayed images, the assessments were (1) change in the FDG uptake position, (2) change in FDG uptake degree, and (3) likelihood of malignancy. The results of FOBT were analyzed independently of the visual interpretations.
Results Interobserver agreement (κ) was 0.501 for assessing FDG uptake patterns, while agreement on assessing changes in uptake degree and changes in uptake position between early and delayed imaging were low ($\kappa =$ 0.213–0.229). Logistic regression analysis indicated that 'FDG uptake patterns' and 'FDG uptake degree' were significantly related to decide on the suspicion of malignancy ($p < 0.001$) and the final result ($p < 0.001$). "Small localized" and "large irregular localized" types had a high probability of a lesion regardless of either (1) FDG uptake degree or (2) variation in the uptake between the early and the delayed image. The delayed image decreased false-positive cases for some FDG uptake patterns, but it had

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little impact on distinguishing clearly between "cancer or adenoma" and "normal". The addition of FOBT had little impact on the diagnosis.

Conclusion There was highest agreement among readers with respect to the recognition of specified colonic FDG uptake patterns, and this pattern recognition had the most influence on the diagnosis. "Small localized" and "large irregular localized" types had a high probability of a lesion. The addition of delayed imaging and of FOBT results to the early imaging did not have much impact on the diagnosis.

Keywords Colonic FDG uptake · PET · Colorectal cancer · Observer validation study · Fecal occult blood testing (FOBT) · Dual-time-point PET

Introduction

Incidental colonic FDG uptake on PET examination is often problematic throughout the diagnostic process. Colonic FDG uptake does not always indicate a malignancy, since FDG uptake can be seen in a variety of conditions, such as physiological variations, adenomas, and inflammatory lesions [1]. Thus, PET is not recommended for screening of colonic malignancy but rather for cancer staging that is related to the detection of regional lymph nodes and distant metastases. On the other hand, colonic FDG uptake has been seen in 1.3 % [2] to 3.0 % [3] of PET scans, and half [2] to two-thirds [3] of these patients were subsequently diagnosed with an unsuspected colonic carcinoma or adenoma [4]. Therefore, it appears that colonic FDG uptake should not be ignored since it has the potential for indicating malignancy. Although the mechanism of FDG uptake in the colon is still unclear, colonic FDG uptake has been compared to pathological assessment [5–10]. However, colonic FDG uptake shows a variety of patterns in form and degree. Tatlidil et al. [11] reviewed the pattern of colonic FDG uptake in 27 patients by classifying them into 4 FDG uptake patterns and 4 grades of FDG uptake. Cases of nodular-focal FDG uptake consisted of abnormal lesions that were either malignant or benign. Those with segmental FDG uptake mainly consisted of colitis. Those with diffuse FDG uptake were noncancerous. However, the number of subjects in the cited study was relatively small, and the study was dominated by cases showing intense FDG uptake (78 % of cases). The results of the study are considered the reference for assessment of colonic FDG, but further evaluation with a larger number of cases and by current experienced readers are needed to illuminate the questions that remain about colonic FDG uptake.

The purpose of the present study was to evaluate the interpretations of incidental colonic FDG uptake made by 10 experienced readers and to more clearly identify the pattern of suspicious colonic FDG uptake. In addition, we wanted to examine whether a second FDG-PET time point or immune fecal occult blood testing (FOBT) could contribute to increasing the diagnostic accuracy of incidental colonic FDG uptake.

Materials and methods

Study design

All study protocols in this retrospective observation study were approved by the institutional review board of Yokohama City University. The cases for evaluating colorectal FDG uptake were taken from FDG-PET scans carried out as cancer screening of asymptomatic subjects at three PET centers in Japan. From 2003 to 2009, 24,295 PET scans were performed in the three PET centers. Abnormal incidental colonic FDG uptake was identified in 354 cases (1.5 %) by a physician specializing in nuclear medicine at each facility, and colon cancer was confirmed in 103 cases (0.4 %).

Inclusion criteria for our study were: (1) in addition to the early scan, a delayed scan at 120 min after FDG injection; (2) FOBT using fecal samples collected on two consecutive days; (3) age $\geq$40 years; (4) blood glucose level <120 mg/dl at the time of the PET scan; (5) no history of any cancer; and (6) final pathological diagnosis for colorectal lesion had been obtained by surgery and/or colonoscopy or by at least 2-year follow-up without cancer development.

According to the criteria, 147 sites in 126 subjects (71 males, 55 females; average age 61.2 years, range 42–87 years) with colorectal FDG uptake were selected for visual interpretation, consisting of 38 FDG uptake sites of

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cancer, 43 uptake sites of adenoma, and 66 uptake sites which were proven not to represent an abnormal lesion. The mean glucose level of the 126 subjects was 97.0 mg/dl.

The diagnosis of colorectal FDG uptake in the 147 sites was established by colonoscopy in 117 sites, surgery in 12 sites, and at least 2 years of observation in 18 sites. If the case had colonic FDG uptake on the first FDG scan and no lesion was confirmed within 2 or 3 years of observation after the first scan, any colorectal FDG uptake observed at the first scan was regarded as "normal".

PET image interpretation

All 147 sites with colorectal FDG uptake were evaluated on the basis of visual inspection by each of 10 experienced, board-certified, nuclear medicine physicians with various degrees of experience with PET imaging diagnosis: 5 years for 3 physicians (S.K., Y.S., M.M); 6 years for 2 physicians (K.I., H.O.); 8 years for one physician (K.O.); 9 years for one physician (K.K.); and 10 or more years for 3 physicians (K.U., T.N., T.T.). All reconstructed PET images were reviewed on a Vox-Base SP1000 workstation (J-MAC Systems, Sapporo, Japan), and the interpretation was based on transaxial, sagittal, coronal, and maximum intensity projection (MIP) views with grayscale images. The observers were requested to make an interpretation and assess the likelihood of malignancy either on the early or the delayed scan. If the image was obtained by PET/CT, only the PET image was provided for observers to evaluate.

At the time of PET image interpretation, the observers were provided with the patient's (1) age, (2) sex, (3) and blood glucose level, and (4) the FDG uptake region for interpretation. The aim of interpretation was not to screen the FDG uptake, but to assess the specific incidental colonic FDG uptake. Therefore, the FDG uptake for interpretation for each case was indicated on a print-out, which was only used to identify the FDG uptake region for interpretation; the visual assessment was performed based on the viewer images mentioned above.

Assessed for the early scan were: (1) FDG uptake pattern (small localized, large irregular localized, short segmental, and long segmental); (2) FDG uptake degree (very high, high, moderate, and slight); and (3) likelihood of malignancy (highly likely, likely, possibility of malignancy, possibility of benign lesion, no abnormality). Assessed for the delayed scan were: (1) change in FDG uptake degree (increased, stable, decreased, and unconfirmed; (2) change in the FDG uptake position (moved or unmoved); (3) and likelihood of malignancy (highly likely, likely, possibility of malignancy, possibility of benign lesion, no abnormality) based on the interpretation of the delayed scan.

Before starting the study, these image interpretation criteria were discussed by all readers. Observers shared a common understanding that "small localized FDG uptake" was small solitary nodular FDG uptake, "large irregular localized FDG uptake" was large solitary FDG uptake indicating the existence of a mass lesion, "short segmental FDG uptake" was FDG uptake along a short reach of colon, and "long segmental FDG uptake" was FDG uptake along a long reach of colon. The representative FDG-PET images for every FDG uptake pattern and FDG uptake degree, some of which are shown in Fig. 1, were selected by agreement of all readers. All readers carried out the interpretation of FDG-PET images by consulting these images.

For each case, a 'consensus interpretation' was determined in one of two ways. It was the choice selected by five (the majority) of the readers, if that number or more agreed on a given choice. If no such agreement existed, the case was then re-reviewed by the three most experienced physicians (S.J., T.Y., E.T.) together; the choice they agreed on became the 'consensus interpretation'. Then, the interpretations of "likelihood of malignancy" were reclassified into just two groups. The first group was called "suspicious for malignancy" and was composed of cases probably malignant (the two original designations "highly likely" and "likely") and cases only suspicious of malignancy (the original designation "possibility of malignancy"). The second group was called "malignancy unlikely" and was composed of the two original designations "possibility of benign lesion" and "no abnormality".

Quantitative analysis was performed by using maximum standardized uptake value (SUV_{max}), with regions of interest (ROIs) drawn over each colonic FDG uptake for interpretation. The analysis was performed independently to the interpretation of the observers. It was aimed at the verification of the result of visual observation. The SUV was classified according to 4 categories (very high, high, moderate, and slight).

"The category FOBT-positive" was defined as at least one positive FOBT test among the two FOBT tests. If the consensus interpretation in PET imaging was combined with FOBT, "positive" was defined as at least one positive result. The results of FOBT testing were not provided to the observers. Likewise, FOBT tests were analyzed independently.

PET scans

Of the 126 PET scans, 93 had been performed using the GE Advance Nxi in two-dimensional mode, with emission scans and transmission scans per bed of 2 and 1 min, respectively, starting at 60 min for the early scan and 120 min for the delayed scan after administration of 3.7 MBq/kg FDG. The scans were corrected for decay, scatter, and randoms and reconstructed using ordered

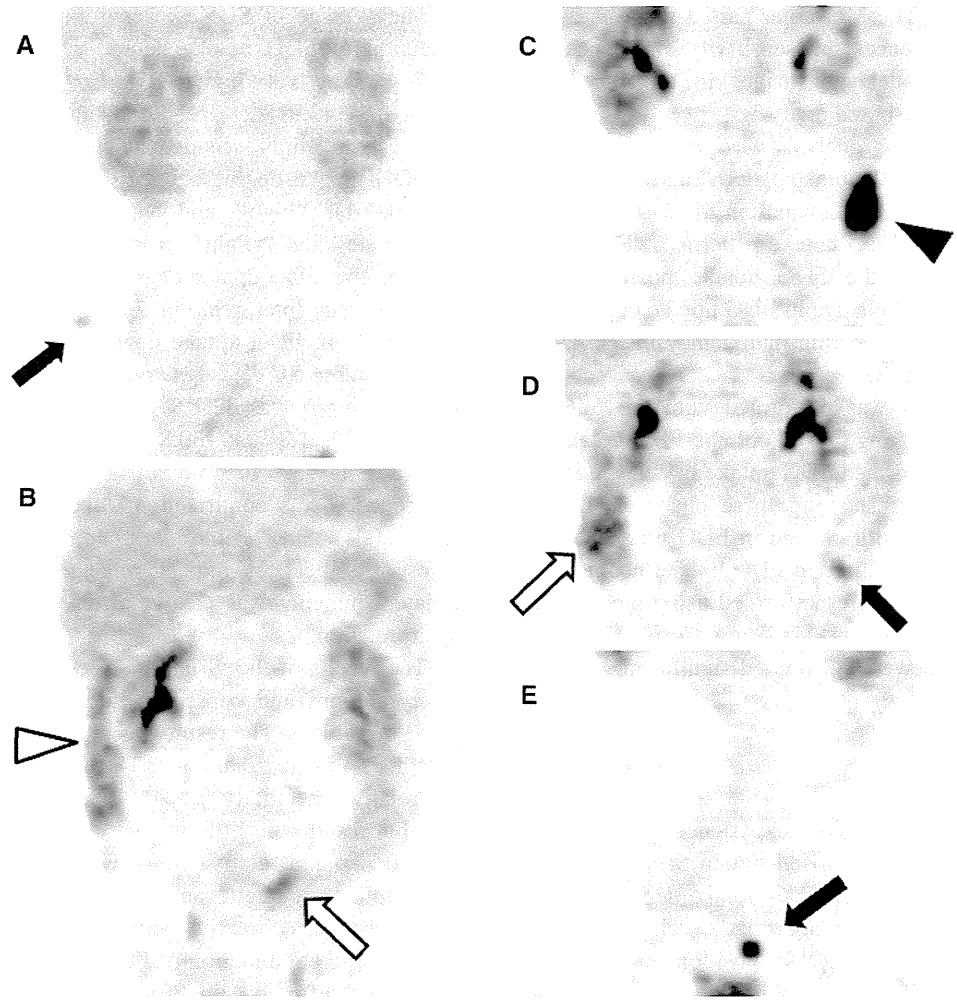

Fig. 1 **a** (*arrow*) Uptake pattern: small localized, Uptake degree: slight. **b** (*white arrow head*) Uptake pattern: long segmental, Uptake degree: moderate (*white arrow*) Uptake pattern: short segmental, Uptake degree: moderate. **c** (*arrow head*) Uptake pattern: large irregular localized, Uptake degree: very high. **d** (*white arrow*) Uptake pattern: short segmental, Uptake degree: moderate (*arrow*) Uptake pattern: small localized, Uptake degree: moderate. **e** (*arrow*) Uptake pattern: small localized, Uptake degree: high

subset expectation maximization (OSEM) with two iterations. In the other 33 cases, 2 PET/CT scanners were used: the GE Discovery ST Elite performance in three-dimensional mode with emission scans per bed of 2 min and reconstructed using OSEM; and the Philips Gemini GXL in three-dimensional mode with emission scans per bed of 2 min and reconstructed using 3D-line of response (LOR). PET/CT scanning was carried out with the same timing as above after 4.5 MBq/kg FDG administration. All PET studies were performed with at least 4 h of fasting prior to the FDG injection.

Statistical analysis

Levels of interobserver agreement were quantified using kappa values (κ values) [12]. The higher the kappa value, the better is the agreement between the observers. Bootstrapping was used to calculate 95 % confidence intervals. The averages of SUV_{max} for colonic FDG uptake were expressed in terms of mean ± standard deviation (SD), and Mann–Whitney *U* test was used to evaluate the differences between categories of visual interpretation. The percent change in the SUV_{max} of colonic FDG uptake between early and delayed image was calculated for the purpose of comparing the visual interpretation of FDG uptake change in the delayed image with the change ratio of SUV_{max}. The Mann–Whitney *U* test was applied to determine the significant difference of SUV_{max} change in each category of visual interpretation.

The differences in the PPV and NPV were analyzed using a marginal logistic regression model. The sensitivity and specificity obtained were regarded as relative values because of the selection bias in the study cases. Thus, the terms "relative sensitivity" and "relative specificity" are

used in our report. The McNemar paired test was used to evaluate the differences in sensitivity and specificity between early and delayed images in terms of visual analysis and location-based analysis.

A logistic regression analysis was performed with the following factors: "FDG uptake pattern" and "FDG uptake degree" for suspecting malignancy in the early image and the final result, and "FDG uptake patterns", "FDG uptake degree", "change in the FDG uptake position in the delayed image", and "change in FDG uptake degree in the delayed image" for suspecting malignancy in the delayed image and the final result.

A Chi-square test was performed with the following status: "the case showing moved colonic FDG uptake", or "decreased or unconfirmed FDG uptake in delayed image" and the case without showing these change in delayed image, and the case with change in FDG uptake position and the case without change in FDG uptake position.

Statistical analyses were performed using the statistical package Stata (version IC 11; Stata Corp, TX, USA). Values of $p < 0.05$ were considered significant.

Results

Re-review by the three most experienced physicians to reach an agreement was carried out in 5 cases for FDG uptake patterns, 8 cases for FDG uptake degree, 11 cases for FDG uptake degree change on the delayed image, 8 cases for change of FDG uptake position on the delayed image, 8 cases for likelihood of malignancy on the early image, and 1 case for likelihood of malignancy on the delayed image.

Interobserver agreement among the 10 readers for each index is summarized in Table 1. The interobserver κ values was 0.501 for assessing the FDG uptake pattern on the early image, This agreement was better than that for uptake degree on the early image or for either of the two categories on the delayed image. However, the interobserver κ value for suspected malignancy was higher with the delayed image ($\kappa = 0.518$) than with the early image ($\kappa = 0.489$).

Table 1 Result of interobserver agreement

Image	Interpretation	κ	95 % CI
Early	FDG uptake pattern	0.501	0.456–0.516
	FDG uptake degree	0.310	0.286–0.326
	Suspected malignancy	0.489	0.473–0.511
Delayed	Change of uptake degree	0.229	0.209–0.241
	Change of uptake position	0.213	0.181–0.218
	Suspected malignancy	0.518	0.504–0.523

The average of SUV_{max} according to consensus interpretation of FDG uptake degree was 21.7 ± 9.0 (range 11.2–41.3) at "very high", 9.5 ± 3.0 (6.4–16.8) at "high", 5.5 ± 1.1 (3.9–8.2) at "moderate", and 4.1 ± 0.7 (2.9–5.8) at "slight". Statistical significance was confirmed in FDG uptake degree between "very high" and "high" ($p < 0.001$), "high" and "moderate" ($p < 0.001$) and "moderate" and "slight" ($p < 0.001$). These significances indicate that FDG uptake degree was clearly differentiated by consensus interpretation. For consensus interpretation for change in FDG uptake degree, the average of change ratio (%) for SUV_{max} between the early image and the delayed image was 32.1 % (range −34.0 to 113.3 %) at "increased", 1.8 % (−30.8 to 44.4 %) at "stable", and −30.2 % (−73.1 to 13.8 %) at "decreased". Statistical significance was confirmed in "increased" and "stable" ($p < 0.001$) and "stable" and "decreased" ($p < 0.001$). These significances indicate change of FDG uptake in delayed imaging was clearly differentiated by consensus interpretation.

The results of the visual analyses based on 10 readers' interpretations and consensus interpretations are summarized in Table 2. The result was independent of experience with PET imaging diagnosis. The delayed image increased the relative specificity ($p < 0.02$) compared to early imaging, but resulted in little impact on PPV ($p = 0.50$), NPV ($p = 0.72$), and relative sensitivity. If their interpretation was applied to detect "cancer and adenoma", no significant difference was observed between the early and delayed images. The combination of FOBT showed no statistically significant difference in PPV and NPV compared to any PET image. The combination of FOBT and the early image for detecting cancer decreased relative specificity ($p < 0.001$) compared to the early image alone. The combination for detecting cancer and adenoma increased relative sensitivity ($p < 0.001$) but decreased specificity ($p < 0.005$) compared to the early image alone. The combination of FOBT and the delayed image for detecting cancer decreased relative specificity ($p < 0.001$) compared to the delayed image alone. The combination for detecting cancer and adenoma increased relative sensitivity ($p < 0.003$) compared to the delayed image alone (Table 2).

Logistic regression analysis based on consensus interpretation showed that 'FDG uptake pattern' and 'FDG uptake degree' were significantly related to the decision about suspecting malignancy and the final result ($p < 0.001$). The change in the FDG uptake degree on the delayed image influenced the suspicion of malignancy on the combined delayed image ($p < 0.001$), in contrast to the lack of effect of FDG uptake position change on the delayed image ($p = 0.08$). The delayed image did not have a significant relation to the final result (FDG uptake degree changed on the delayed image, $p = 0.79$; FDG

Table 2 Results of visual analysis

Lesion type	Imaging	Interpretation	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Cancer	Early	10 readers	29.1–40.3	86.1–97.4	71.1–97.4	22.0–57.8
		Consensus	33.0	92.7	92.1	34.9
		Consensus + FOBT	31.7	100.0	100.0	22.8
	Delayed	10 readers	28.1–49.2	82.9–94.7	76.3–94.7	20.1–57.8
		Consensus	37.6	94.4	92.1	46.8
		Consensus + FOBT	33.0	97.1	97.4	31.2
Cancer and adenoma	Early	10 readers	59.8–74.0	62.5–79.5	65.4–92.6	28.0–69.7
		Consensus	65.1	70.7	86.4	43.9
		Consensus + FOBT	62.5	77.8	92.6	31.8
	Delayed	10 readers	57.9–84.5	53.8–71.1	65.4–87.6	22.7–83.3
		Consensus	69.9	70.4	80.2	57.6
		Consensus + FOBT	64.3	74.3	88.9	39.4

The results from 10 readers are represented by the range

PPV positive-predictive value, *NPV* negative-predictive value, *FOBT* fecal occult blood test

Table 3 Results of logistic regression analysis

Image	FDG uptake	*p* value	Subject
Early	FDG uptake patterns	<0.001	Suspected malignancy in early image
		<0.001	Final result
	FDG uptake degree	<0.001	Suspected malignancy in early image
		<0.001	Final result
Delayed	Change of uptake degree	<0.001	Suspected malignancy in early image
		0.79	Final result
	Change of uptake position	0.08	Suspected malignancy in early image
		0.37	Final result

uptake position changed on the delayed image, $p = 0.37$) (Table 3).

The results of interpretations based on location are summarized in Table 4. Region-based analysis on the early image had a low PPV in the all areas of the colon, except the rectal region. The delayed image tended to increase PPV and relative specificity for judging "cancer" and "cancer and adenoma". However, no statistically significant difference between the early and delayed images was found for all the regions.

The results for the lesions based on visual interpretations are summarized in Table 5. Small localized FDG uptake included a large number of cancers, but the relative specificity was low because the FDG uptake pattern included a large number of adenomas. The large irregular localized type and the very high FDG uptake were relatively specific to cancer.

Delayed imaging did not improve the results in cases of small and large, irregular, localized FDG uptake (Table 6). The incidences of "decreased", "unconfirmed", and "moved" classifications for the delayed image were small in number, but tended to exclude normal cases preferentially. If the cases with "decreased" "unconfirmed" or "moved" were excluded (Table 6, exclusion A), 40.0 % (16/40) of normal cases within short segmental pattern or long segmental pattern, and 27.6 % (16/58) of normal cases showing over moderate FDG uptake could be reduced. However, delayed imaging did not contribute to distinguishing the cancerous from the noncancerous case for any FDG uptake pattern observed in the early imaging ($p \geq 0.16$).

Discussion

The present study assessed observer variation in characterizing incidental colonic FDG uptake. Interobserver agreement was highest for assessing the FDG uptake pattern, and "small localized" and "large irregular localized" patterns had high probabilities of colon cancer regardless of FDG uptake degree and variation in the uptake on the delayed image. The delayed image contributed to decreasing false-positives when either "short segmental" or "long segmental" FDG uptake on the early image was confirmed.

Colonic FDG uptake shows a variety of patterns in form and degree. In the present study, the result of interpretation was not based on individual experience but rather a consensus judgment. Thereby, we sought to establish a strategy for diagnosing incidental colonic FDG uptake that was robust. Tatlidil et al. [11] reviewed the patterns of colonic FDG uptake by classifying them into 4 FDG uptake patterns and 4 grades of FDG uptake. However, determining

Table 4 Results of region-based analysis based on consensus interpretation

Lesion	Region	Number				Early				Delay			
		To	Ca	Ad	Nor	PPV (%)	NPV (%)	Sen (%)	Spe (%)	PPV (%)	NPV (%)	Sen (%)	Spe (%)
Cancer	Cecum	14	2	1	11	22.2	100.0	100.0	41.7	33.3	100.0	100.0	66.7
	Ascending	38	10	11	17	35.7	100.0	100.0	35.7	43.5	100.0	100.0	53.6
	Transverse	7	2	2	3	25.0	66.7	50.0	40.0	25.0	66.7	50.0	40.0
	Descending	21	5	7	9	26.7	83.3	80.0	31.3	30.8	87.5	80.0	43.8
	Sigmoid	44	9	15	20	27.3	100.0	100.0	31.4	28.6	93.8	88.9	42.9
	Rectum	23	10	7	6	52.9	83.3	90.0	38.5	52.6	100.0	100.0	30.8
Cancer and adenoma	Cecum	14	2	1	11	33.3	100.0	100.0	45.5	50.0	100.0	100.0	72.7
	Ascending	38	10	11	17	57.1	50.0	76.2	29.4	69.6	66.7	76.2	58.8
	Transverse	7	2	2	3	75.0	66.7	75.0	66.7	75.0	66.7	75.0	66.7
	Descending	21	5	7	9	66.7	66.7	83.3	44.4	76.9	75.0	83.3	66.7
	Sigmoid	44	9	15	20	69.7	90.9	95.8	50.0	64.3	62.5	75.0	50.0
	Rectum	23	10	7	6	82.4	50.0	82.4	50.0	78.9	50.0	88.2	33.3

To total, *Ca* cancer, *Ad* adenoma, *Nor* normal, *PPV* positive-predictive value, *NPV* negative-predictive value, *Sen* sensitivity, *Spe* specificity

Table 5 Results of consensus visual interpretation based on FDG uptake pattern

Interpretation	FDG uptake pattern														
	Small localized			Large irregular			Short segmental			Long segmental			Total		
	Ca	Ad	Nor	Ca	Ad	Nor	Ca	Ad	*N*	Ca	Ad	Nor	Ca	Ad	Nor
Total	22	31	22	13	2	4	2	6	28	1	4	12	38	43	66
FDG uptake degree															
Very high	1	1	0	6	0	0	0	0	1	0	0	0	7	1	1
High	15	16	7	7	2	4	2	4	15	0	2	5	24	24	31
Moderate	3	11	13	0	0	0	0	2	9	0	1	4	3	14	26
Slight	3	3	2	0	0	0	0	0	3	1	1	3	4	4	8
Change of uptake degree															
Increased	13	25	13	9	1	2	2	2	13	1	2	8	25	30	36
Stable	7	3	8	3	1	1	0	2	7	0	2	4	10	8	20
Decreased	1	3	1	0	0	1	0	2	5	0	0	0	1	5	7
Unconfirmed	1	0	0	1	0	0	0	0	3	0	0	0	2	0	3
Change of uptake position															
Moved	2	4	0	0	0	0	0	3	10	0	0	3	2	7	13
Unmoved	20	27	22	13	2	4	2	3	18	1	4	9	36	36	53

Ca cancer, *Ad* adenoma, *Nor* normal

whether the colonic FDG uptake pattern and FDG uptake degree can be common criteria among readers remained a question. In the present study, 10 readers showed agreement, with $\kappa = 0.501$, for the FDG uptake pattern, for which the interpretation criteria are the more reliable. Confusion of the FDG uptake pattern between "short segmental" and "large irregular localized" might remain an issue. We assumed that the "short segmental" FDG uptake pattern showed FDG accumulation in the shape of the colon, while "large irregular localized" was defined as FDG accumulation beyond the regular colon shape, suggesting the presence of a large mass lesion. In these two FDG uptake patterns, FDG uptake degree was interpreted as being higher in cancer than in other conditions. Among the cases showing the "short segmental" or "large irregular localized" FDG uptake pattern, very high or high FDG uptake had a PPV of 39.0 % and a relative sensitivity of 100.0 % for detecting cancer. Thus, the degree of FDG uptake appears to have some impact on the diagnosis. The present results showed that the delayed image contributed to decreasing false-positives if the FDG uptake pattern was either the "short segmental" or "long segmental" type.

Table 6 Results of consensus visual interpretation in delayed imaging

Interpretation	Total				Exclusion (A)					Exclusion (B)				
	Ca	Ad	Nor	Total	Ca	Ad	Nor	Total	Rate (%)	Ca	Ad	Nor	Total	Rate (%)
FDG uptake patterns														
Small localized ($N = 75$)	22	31	22	75	20	26	21	67	4.5	20	27	22	69	0.0
Large irregular ($N = 19$)	13	2	4	19	12	2	3	17	25.0	13	2	4	19	0.0
Short segmental ($N = 36$)	2	6	28	36	2	2	15	19	46.4	2	3	18	23	35.7
Long segmental ($N = 17$)	1	4	12	17	1	4	9	14	25.0	1	4	9	14	25.0
FDG uptake degree														
Very high ($N = 9$)	7	1	1	9	7	1	0	8	100.0	7	1	0	8	100.0
High ($N = 79$)	24	24	31	79	23	17	24	64	22.6	24	19	27	70	12.9
Moderate ($N = 43$)	3	14	26	43	3	14	18	35	30.8	3	14	19	36	26.9
Slight ($N = 16$)	4	4	8	16	2	2	6	10	25.0	2	2	7	11	12.5

Total and after applying exclusion criteria

Exclusion (A): exclusion of decreased, unconfirmed, or moved in delayed image

Exclusion (B): exclusion of moved in delayed image

Rate (%): reduction rate of normal cases by delayed imaging

Ca cancer, *Ad* adenoma, *Nor* normal

Although the delayed image had little influence on cases classified as "large localized" on the early image, FDG uptake that did not move on the delayed image might contribute substantially to reducing false-positive cases when the FDG uptake pattern was difficult to differentiate between "short segmental" and "large irregular localized".

The measurement of the standardized uptake value (SUV) is valuable to define the degree of FDG uptake. However, SUV is affected by factors such as the size of the ROI, the reconstructed resolution of the PET image, body mass index, and serum glucose level; it appears to be difficult to define a diagnostic cut-off value for FDG uptake by SUV [13]. "Very high" or "high" FDG uptake did include the majority of cancers and adenomas. For the two classifications of "very high and high" and "moderate and slight" for FDG uptake, interobserver agreement among the 10 readers was estimated to be 0.485 (95 % CI, 0.436–0.505), which might be regarded as acceptable.

On visual analysis, the rectosigmoid colon, cecum, and proximal ascending colon show higher levels and a more variable pattern of FDG uptake compared with other colonic regions [14]. This result might be related to the present result that showed low PPV for the colon excepting the rectum.

Colonic adenomas are regarded as precursors of colorectal cancer [15], and an adenoma–carcinoma sequence is a widely accepted theory [16]. Thus, screening and removal of adenomatous polyps are significant aspects of prevention and improvement of prognosis [17]. The establishment of reliable screening tests for adenomas increases the chance of patients undergoing colonoscopic examination or surgery to remove advanced adenomas before they become malignant [18–20]. However, adenomas have a low probability of malignant transformation, taking an average of 10 years, and the probability depends on the size. Therefore, the clinical importance of screening adenomas is to detect advanced adenomas, defined as adenomas with a diameter of 10 mm or greater, or high-grade dysplasia. The usefulness of FDG-PET for colonic adenoma detection has been previously reported [5, 6, 21, 22], and the sensitivity of FDG-PET depended on the size and histologic grade of the adenoma [1, 11]. Thus, FDG-PET has a high probability for detecting adenomas that should be removed. The present results show that FDG-PET has a high relative sensitivity for either cancer or adenoma. Small and large irregular localized FDG uptake patterns were common in cancers and adenomas. Moreover, large irregular localized FDG uptake was frequently seen in cancer. The FDG uptake degree was higher in cancer than in adenoma, but they overlapped considerably in "high accumulation", which also included normal areas. These results indicate that the FDG uptake pattern of cancer has much in common with that of adenoma, resulting in difficulty differentiating between cancer and adenoma.

PET/CT provides exact localization of FDG uptake, which is more accurate than PET and/or CT [23]. PET/CT contributes to the evaluation of colonic FDG uptake by not only providing the anatomical location, but also by showing the CT finding [1, 4]. Since a large colorectal tumor can be identified by the CT finding, PET/CT might contribute to evaluation of cases showing "short segmental" or "large irregular localized" uptake. However, the CT image is not sufficient if the suspected malignant lesion is not well defined on the image [24]; thus, the findings of

characteristic colonic FDG uptake can help in developing a more accurate method.

Randomized trials have shown that FOBT reduces colorectal cancer mortality by up to 16 % [25–28]. However, the sensitivity and specificity of FOBT have remained problematic, even though FOBT is a noninvasive and cost-effective test [29]. In the present study, the result of FOBT alone scored a higher PPV and relative specificity, and a lower NPV and relative sensitivity than FDG-PET. The result of combined FDG-PET and FOBT tended to increase NPV and relative sensitivity but had lower PPV and relative specificity than the individual tests. Thus, the contribution of FOBT as an index for colorectal FDG uptake is low in terms of lowering the NPV and specificity, leading to unnecessary further testing.

Dual-time-point PET imaging has been reported to have the potential for differentiating between malignant and benign lesions, because FDG uptake in malignant lesions tends to be higher on delayed imaging than on the early imaging [30–35]. The potential for dual-time-point FDG-PET imaging for the colonic region has not been sufficiently evaluated. The present results show that delayed imaging decreased the relative sensitivity for detecting cancer in the sigmoid colon. Toriihara et al. [36] reported that physiological FDG uptake on delayed imaging was increased in the colon region, and it might have affected the present result. Moreover, the present results show that dual-time-point FDG-PET imaging does not contribute to detecting adenoma and differentiating between cancer and adenoma. FDG uptake was relatively lower for adenoma than for cancer, so that FDG uptake for adenoma may be affected by variations in physiological FDG uptake.

This study involved only subjects who had incidental colonic FDG uptake on PET examinations. Thus, the present result does not reflect on the potential of FDG-PET for screening for colon lesions, because PET-negative colon lesions were not included in the present study. In addition, since delayed images can sometimes clearly show a colon lesion regardless of being PET-negative on the early image, the present conclusions about delayed imaging are limited to lesions with incidental FDG uptake detected on an early image.

A limitation of this study was the absence of cases with symptomatic, non-neoplastic diseases, such as inflammatory enterocolitis, collagen colitis, and diverticulitis. Intraobserver variability was not examined, and a prospective study for validation should be done.

Conclusion

The present study assessed incidental colonic FDG uptake by studying observer variation. Interobserver agreement was highest for assessing FDG uptake patterns, and "small localized" and "large irregular localized" types were associated with high probabilities of colon cancer regardless of FDG uptake degree and variations in the uptake on delayed images. Although the delayed image decreased false-positive cases for some FDG uptake patterns on the early PET image, delayed imaging and also the addition of an FOBT result to FDG-PET did not have much impact on the patient diagnosis afforded by colonic FDG uptake.

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ORIGINAL ARTICLE

Standardization of image quality across multiple centers by optimization of acquisition and reconstruction parameters with interim FDG-PET/CT for evaluating diffuse large B cell lymphoma

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Abstract
Objective A multicenter trial is currently underway using FDG-PET/CT to evaluate diffuse large B cell lymphoma in Japan (JSCT NHL10). Standardization of the image quality between the participating centers is a fundamental aspect of the study. Within the framework of JSCT NHL10, standardization of the image quality was attempted by optimizing the acquisition and reconstruction conditions using mid-therapy FDG-PET/CT for diffuse large B cell lymphoma. This report describes the procedures and results of this attempt.
Methods The acquisition protocols and imaging quality were initially determined at each center and again after modification. The image quality was based on performance with an ^{18}F-filled National Electrical Manufacturers Association standards body phantom. We determined that the acquisition duration and reconstruction parameters of each scanner evaluated were in compliance with the

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