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Review

이차성 원발암에서의 ^{18}F-FDG PET/CT의 이용

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Use of ^{18}F-FDG PET/CT in Second Primary Cancer

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This review focuses on the use of ^{18}F-FDG PET/CT to evaluate second primary cancers. The emergence of a second primary cancer is an important prognostic factor in cancer patients. The early detection of a second primary cancer and the appropriate treatment are essential for reducing the morbidity and mortality associated with these tumors. Integrated ^{18}F-FDG PET/CT, which can provide both the metabolic and anatomic information of a cancer, has been shown to have a better accuracy in oncology than either CT or conventional PET. The whole body coverage and high sensitivity of ^{18}F-FDG PET/CT along with its ability to provide both metabolic and anatomic information of a cancer make it suitable for evaluating a second primary cancer in oncology. Whole body ^{18}F-FDG PET/CT is useful for screening second primary cancers with a high sensitivity and good positive predictive value. In order to rule out the presence of a second primary cancer or an unexpected metastasis, further diagnostic work-up is essential when abnormal findings indicative of a second primary cancer are found on the PET/CT images. PET/CT is better in detecting a second primary tumor than conventional PET. (Nucl Med Mol Imaging 2007;41(3):185-193)

Key Words: second primary cancer, staging, ^{18}F-FDG, PET, PET/CT

Introduction

Cancer is one of the leading causes of death in many countries including Korea. The 5-year relative survival rate after a diagnosis of cancer has increased steadily over the last few decades. The number of cancer survivors has tripled since 1971 and is growing by 2% each year due to advances in early detection, diagnostic methods, supportive care, and treatment.[1] The National Cancer Institute recently estimated that on January 1, 2002, 10.1 million Americans were alive with a history of invasive cancer, representing 3.5% of the population.[2] One of the most serious events experienced by cancer survivors is the occurrence of a new cancer. Second primary cancers have become an increasing concern in oncology. This is because with the increased survival of cancer patients, more than 10 percent of all invasive cancers are second or later primary cancers, which comprise the fifth most common group of malignancies after prostate, breast, lung, and colorectal cancers in the Unites States.[2] The emergence of a second primary cancer is an important prognostic factor in cancer patients. A second primary cancer is the leading cause of treatment failure and death in many types of malignancies including early stage head and neck squamous cell carcinomas[3] and Hodgkin's disease.[4] Cancer survivors have approximately double the probability of developing a new primary cancer than a cancer-free individual of the same age and gender.[5] In survivors of childhood cancer, this risk of second primary cancers is 3-6 times higher than the general population.[6] Furthermore, second primary cancers frequently arise in unfavorable sites, such as the esophagus, which has a poor prognosis, as

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well as in previously treated or in areas where an early diagnosis is difficult.[3,5,7] In this context, the early detection of a second primary cancer and the appropriate treatment are essential for reducing the morbidity and mortality associated with these tumors. This is particularly so in symptom-free patients, which is quite common. Conventional radiological methods such as simple radiography and computed tomography (CT) are unsuitable due to the relatively low sensitivity and limited field of coverage. Therefore, a new diagnostic method is needed to efficiently screen a second primary cancer.

Whole body positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is good for diagnosing, staging, restaging and evaluating the prognosis of many malignant tumors on account of their increased glucose utilization than normal tissues.[8] A combined PET/CT scanner was recently developed, which consisted of a PET scanner and a CT scanner within a single device.[9] Acquiring both CT and PET images in the same scanner obviates the need for software registration and routinely provides accurately aligned images of the anatomy and function in a single scan. Integrated ^{18}F-FDG PET/CT, which can provide both the metabolic and anatomic information of a cancer, has been shown to have a better accuracy in oncology than either CT or conventional PET.[10] The whole body coverage and high sensitivity of ^{18}F-FDG PET/CT along with its ability to provide both metabolic and anatomic information of a cancer make it suitable for evaluating a second primary cancer in oncology. This review focuses on the use of ^{18}F-FDG PET/CT to evaluate second primary cancers.

Definitions

A second primary cancer is defined as a histologically or molecularly distinct cancer that develops after the first diagnosed cancer. The criteria for a second primary cancer were established in 1932 as follows: 1) both tumors are histologically malignant; 2) the two cancers are anatomically separated, and not connected by either submucosal or intraepithelial neoplastic changes; and 3) the possibility that one tumor represents metastasis from the other is excluded. Some authors used the term "double primary cancers" or "second primary tumors" to refer to second primary cancers.[11]

The first diagnosed cancer is called the index tumor, and a second primary cancer is any malignancy detected thereafter. Second primary cancers are classified as either synchronous and metachronous. Second primary cancers are synchronous if they are diagnosed at the same time as the index tumor such as during the initial evaluation or during the staging of the index tumor, or within 6 months after the discovery of the index tumor. Some authors used the term "simultaneous primary tumor" to refer to synchronous second primary cancers diagnosed at the some time as the index tumor such as during the initial evaluation or staging of the index tumor, or within 1 month after discovering the index tumor. A second primary cancer is classified as metachronous if it is detected after a follow-up period of 6 months.

Conventional ^{18}F-FDG PET

^{18}F-FDG PET has several advantages in evaluating a second primary cancer compared with conventional diagnostic procedures. Firstly, it provides whole body images. Usually, the PET scan protocol covers the body between the basal skull and mid thigh, which include the sites where most cancers occur. In contrast, the conventional diagnostic work-up usually focuses on a specific region (e.g. chest CT for thorax) or organ (e.g. sigmoidoscopy for rectosigmoid colon). Secondly, PET is a functional metabolic imaging modality. Its high sensitivity in depicting increased metabolism in a wide variety of malignancies adds significant accuracy to many diagnostic regimens compared with anatomic imaging only.

The first report showing the potential value of ^{18}F-FDG PET in a second primary cancer was published in 1997.[12] Among 66 patients initially diagnosed with head and neck cancers, PET showed abnormal thoracic uptake in 10 patients (15.2%), which was demonstrated to be malignant only in 3 cases (4.5%) including 2 cases also found using a conventional routine staging work-up. They concluded that ^{18}F-FDG PET had a very low yield of 1.5% (1/66) in identifying unexpected synchronous second primary cancer. However, their study had several limitations. They

performed a PET scan only from the head to the thorax, not the whole body. In addition, pathological confirmation was not carried out in the 7 of 10 cases with an abnormal ^{18}F-FDG thoracic uptake due to its retrospective design.

The first prospective study dealing with the use of ^{18}F-FDG PET to identify a simultaneous primary cancer was published in 1999.[13] The authors prospectively studied a case series of 68 consecutive patients with a primary tumor in the oral cavity or oropharynx. The clinical or conventional staging work-up detected a second simultaneous primary malignant tumor in 5 of the 68 patients (4.7%). In contrast, ^{18}F-FDG PET was able to identify a second simultaneous primary malignant tumor in 12 of the 68 patients (17.6%; 6 in head and neck, 5 in lung and 1 in thyroid) including the 5 patents detected using the clinical or conventional staging work-up. Therefore, ^{18}F-FDG PET had a significantly higher rate of detection of simultaneous primary tumors than clinical or conventional staging work-up. More importantly, there were no patients with additional simultaneous or synchronous primary tumors found during the follow-up. Their study highlighted the utility of ^{18}F-FDG PET to detect a second simultaneous primary cancer for the first time. However, their study had the same limitation as previous study in that the PET scan covered only the head to chest, not the whole body. Therefore, the authors could not report the presence of a second primary cancer occurring below the diaphragm.

Whole body ^{18}F-FDG PET for evaluating a second primary cancer was used for the first time in 2000.[14] Among 106 patients with squamous cell carcinoma of the oral cavity, whole body ^{18}F-FDG PET identified 7 unexpected distant metastases (6.6%) and 3 synchronous second primary cancers (2.8%) including the esophagus, stomach and skin, which were not detected by conventional staging work-up. In the reconstruction of a PET image, attenuation correction with an additional transmission scan is essential in order to compensate for the interaction between the photons and the tissue, which can result in an underestimation of the radioactive counts originating from the tissues deep in the body. However, in their study, attenuation-corrected PET images were available only in head and neck region, which might have decreased the sensitivity of PET in detecting a second primary cancer in other regions. In addition, the authors did not mention the false positive cases of PET for an unsuspected distant metastasis or a second primary malignancy. Therefore, the positive predictive value of PET was not reported.

Nishiyama, et al. also reported that whole body ^{18}F-FDG PET could detect simultaneous primary cancers in patients with an untreated head and neck cancer.[15] PET showed abnormal findings indicative of a second primary cancer or distant metastasis in 10 of their 53 patients (18.9%). Of the 10 patients, 5 (2 in stomachs, 1 in thyroid, 1 in rectum, and 1 in pancreas) were found to have a second primary cancer, and 2 had a distant metastasis. Therefore, the positive predictive value of whole body ^{18}F-FDG PET for a distant metastasis or synchronous second primary malignancy was 70.0% (7/10) in head and neck cancer. PET could not find a prostate cancer in 1 patient detected by the elevated serum prostate specific antigen level. Conventional staging work-up could detect 50% (4/8) of patients with a second primary cancer or a distant metastasis.

In lung cancer, whole body ^{18}F-FDG PET showed good results in identifying an unexpected second primary cancer. Recent multicenter prospective trials reported that distant metastatic disease or a synchronous second primary malignancy, which was not detected either clinically or radiographically, was identified by ^{18}F-FDG PET during the initial staging in 45 of 287 patients (15.7%) with non-small cell lung cancer.[16] Among them, 15 cases (6.6%) were confirmed to be a distant metastasis, and 3 patients (1.0%) were found to have second primary cancers in the colon, lung, and thyroid, respectively. Nineteen cases were false positives for distant metastatic disease. No further diagnostic confirmations were carried out in the remaining 8 cases. Therefore, the positive predictive value of whole body ^{18}F-FDG PET for an unexpected distant metastasis or a synchronous second primary malignancy was 48.6% (18/37) in those with lung cancer.

A recent study suggested the utility of whole body ^{18}F-FDG PET for a second primary cancer in esophageal cancer.[17] Of the 58 patients with initially diagnosed

esophageal cancer, PET indicated an unexpected distant metastasis or synchronous second primary malignancy in 13 patients (22.4%). Of those 13 patients, 8 were confirmed to have an unexpected distant metastasis (12.1%; n=7) and/or second primary malignancy (3.4%; n=2; colon and tonsil). Therefore, the positive predictive value of whole body ^{18}F-FDG PET for an unexpected distant metastasis or synchronous second primary malignancy was 61.5% (8/13) those with esophageal cancer.

Van Westreenen, et al. also reported that whole body ^{18}F-FDG PET can be used to detect unexpected synchronous primary neoplasms in patients with esophageal cancer.[18] Of the 366 patients with a biopsy-proven malignancy of the esophagus, PET identified abnormal foci indicative of synchronous second primary neoplasms in 20 patients (5.5%), of which 15 lesions had not been detected by routine staging work-up. Finally, 10 patients were confirmed to have synchronous second primary cancers (5 in kidneys, 2 in colons, 1 in lung, 1 in thyroid, and 1 in oral cavity). Therefore, the positive predictive value of whole body ^{18}F-FDG PET for an unexpected synchronous second primary malignancy was 50.0% (10/20) in those with esophageal cancer.

Agress, et al. first reported the use of PET to evaluate an unexpected malignancy in subjects with various index tumors in 2004.[19] A total of 1,750 patients underwent whole body ^{18}F-FDG PET to evaluate a variety of known or suspected malignancies. PET identified 58 abnormal unexpected foci of hypermetabolism in 53 patients (3.0%). Of the 42 histopathologically confirmed abnormalities in 37 patients, 30 foci (71.4%) in 25 patients were either malignant (n=12; 3 in colon, 2 in breast, 2 in larynx, 1 in gall bladder, 1 in ovary, 1 in fallopian tube, and 1 in thyroid) or premalignant tumors (18 colonic adenomas) that differed from the cancer that the patient had originally been diagnosed with. Therefore, the positive predictive value of whole body ^{18}F-FDG PET for an unexpected malignancy or precancerous lesion in patients with a known or suspected malignancy was 71.4% (30/42). However, their study had several limitations. First, it is unclear if all subjects had histologically proven malignant index tumors. Therefore, it is difficult to determine if all unexpected malignant lesions detected by PET were second primary cancers. Secondly, a histological confirmation could not be carried out in a considerable number of hypermetabolic lesions (27.6%; 16/58). Thirdly, after excluding premalignant lesions, the positive predictive value of whole body ^{18}F-FDG PET for an unexpected malignancy was only 28.6% (12/42).

In summary, conventional ^{18}F-FDG PET has some value in detecting unsuspected second primary cancers but is not satisfactory. This might result from the inherent disadvantages of conventional PET imaging. Accurate anatomic localization of the functional abnormalities observed on conventional PET scans is a well known challenge due to the lack of a detailed, high-resolution anatomy. In particular, there are many organs with physiological uptakes that can mimic a malignancy such as the salivary glands, laryngeal muscles, gastrointestinal tract, lymphoid tissues etc. Further diagnostic confirmations were not carried out in a statistically relevant number of subjects due to the retrospective design of PET studies. The other problem is that both emission and transmission scans are essential for generating attenuation corrected PET images, which usually require a long scan time of > 50 min for whole body imaging. Some studies did not adopt a whole body PET imaging protocol due to the long scan time required.

Integrated ^{18}F-FDG PET/CT

Recently developed integrated PET/CT has solved the above mentioned problems associated with conventional PET, and has several advantages over conventional PET. Integrated PET/CT is a dual-imaging modality that is capable of hardware fusion between functional and anatomical images.[9] This means that the fusion process between PET and CT images is easier and more accurate than previously used fusion software. Secondly, the CT data is used for the attenuation correction of the PET images, which means that a short CT scan replaces a long transmission scan. This means there is a reduced scan time for whole body imaging (generally less than 30 min) and improved facility efficiency, which makes routine whole body imaging possible. Thirdly, due to high-count statistics in the photon density of CT, a CT-based attenuation map

has less background noise than an attenuation map using a conventional transmission scan. Recent studies reported that PET/CT was more accurate and useful in oncology than PET by providing improved anatomical localization and characterization of lesions, and a subsequent favorable impact on patients' management).[10,20] Therefore, PET/CT is more suitable for detecting second primary cancers than PET.

The first report mentioning the use of whole body ^{18}F-FDG PET/CT to detect unexpected second primary cancers was published in 2003.[21] In 6 out of 48 patients (12.5%) with an initially diagnosed advanced head and neck squamous cell carcinoma, PET/CT found clinically unsuspected lesions suggesting a distant metastasis (n=4) or a synchronous second primary cancer (n=2; lung and colon). A distant metastasis in 2 patients and lung cancer in 1 patient were demonstrated. Therefore, the positive predictive value of whole body ^{18}F-FDG PET/CT for an unexpected distant metastasis or synchronous second primary malignancy was 50.0% (3/6) in those with head and neck cancer.

The same institution in the above study reported subsequent results including the use of post-therapeutic ^{18}F-FDG PET/CT to detect unexpected second primary cancers in head and neck cancer.[22] They examined 26 patients who underwent PET/CT (n=21) or PET (n =5) before and approximately 6 weeks after the end of a combined treatment with radiation and chemotherapy with a curative intent. No patient had a distant metastatic disease or second primary cancer on the initial staging work-up including PET. In 3 of the 26 patients (11.5%), post-therapeutic PET found clinically unsuspected lesions suggesting a distant metastasis (3.8%; n=1; lung and mediastinum) or a synchronous second primary cancer (7.7%; n=2; lung and rectum), which were confirmed to be malignant either histopathologically or clinically. No false positive cases were found in the post-therapeutic ^{18}F-FDG PET/CT used for detecting a clinically unsuspected malignancy.

Ishimori, et al. first reported the use of a whole body PET/CT study to evaluate unexpected additional primary malignancy in subjects with various index tumors in 2005.[23] They examined 1,912 patients who underwent ^{18}F-FDG PET/CT for known or suspected malignant lesions in various sites including the lung (28.6%), colon or rectum (12.4%), head or neck (12.1%), lymph nodes (10.9%), breast (7.6%), gynecological organs (7.1%), genitourinary organs (4.2%), esophagus (3.6%), and skin (melanoma). PET-positive lesions suggestive of new second primary cancers were found in 79 (4.1%) of the 1,912 patients. Further diagnostic confirmation was carried out in 40 patients (50.6%) pathologically (n=32) or by a clinical follow-up (n=8). Of the 40 patients, 22 (1.2% of 1,912 patients) were found to have new primary cancers in lung (n=7), thyroid (n=6), colon (n=4), breast (n=2), esophagus (n=2), bile duct (n=1), and oropharynx (n=1). One patient had two additional cancers in the lung and the thyroid. Therefore, the positive predictive value of whole body ^{18}F-FDG PET/CT for an unexpected additional primary malignancy was 55.0% (22/40). Importantly, in 17 out of 22 patients (77.3%) the treatment plan was changed and the new lesion was surgically resected after the PET/CT examination. However, there were several limitations in their study. Due to its retrospective design, 50% of patients with abnormal PET findings suggesting an additional primary malignancy did not undergo a further diagnostic confirmation or clinical follow-up. It is unclear if all 1,912 subjects had a histologically proven malignant index tumor. Therefore, it is not known if those unexpected additional primary malignant lesions detected by PET/CT were all second primary cancers.

Immediately after Ishimori, et al.'s study, we reported the first prospective study dealing with the use of the whole body ^{18}F-FDG PET/CT to detect synchronous second primary cancer.[24] The subjects were 547 patients diagnosed with cancer (50.5% in lung, 20.7% in esophagus, 10.4% in head and neck, and 6.6% with lymphoma) who underwent ^{18}F-FDG PET/CT imaging for the initial staging. In 26 out of 547 patients (4.8%), a total of 27 second primary malignant tumors were finally identified in the head and neck (n=7), lung (n=5), stomach (n=5), colon (n=3), thyroid (n =3), esophagus (n=2), and gall bladder (n=1). The index tumors were located in the esophagus (53.8%), lung (19.2%), head and neck (15.4%), and others (11.6%). There were 45 lesions in 45 patients

with an abnormal focal ^{18}F-FDG uptake on PET/CT that was indicative of a second primary cancer. Twenty-four of the 45 lesions (53.3%) were found to be second primary cancers. Seven lesions (15.6%: 2 in thyroid, 2 in lung, 1 in kidney, 1 in liver, and 1 in muscle) were unexpected distant metastases that were confirmed by histopathology. The remaining 14 lesions (31.1%: 8 in thyroid, 3 in intestine, 2 in esophagus, and 1 in nasopharynx) were found to be benign. All 3 second primary cancers with false negative PET findings were early gastric cancers in the esophageal cancer patients, which were found only by endoscopy. Therefore, the positive predictive value of ^{18}F-FDG PET/CT for detecting a second primary cancer or an unexpected metastasis was 68.9% (31/45). In contrast, conventional staging work-up did not identify 16 lesions as either a second primary cancer or clinically unexpected metastatic lesion. Therefore, ^{18}F-FDG PET/CT has a high sensitivity of 91.2% (31/34) in detecting a second primary cancer or unexpected metastases, which was significantly higher than the 50% (17/34) obtained from a conventional staging work-up ($p < 0.005$). This study had several advantages over previous reports mentioning the use of PET or PET/CT in evaluating a second primary cancer. First, all the subjects had histologically proven underlying malignant tumors. Therefore, the term second primary cancer can be applied directly to the results. Due to the prospective design, further diagnostic confirmation or clinical follow-up was carried out in most of subjects with abnormal foci of ^{18}F-FDG uptake indicative of a second primary cancer (84.9%, 45/53).

This study has several important clinical implications.[24] The high sensitivity of 91% (100% when excluding gastric cancers) and the good positive predictive value of 69% for detecting a second primary cancer or an unexpected metastasis highlight the value of ^{18}F-FDG PET/CT as a tool for screening a synchronous second primary cancer. The relative high positive predictive value of PET/CT suggests that a further diagnostic work-up is essential in order to exclude the possibility of a second primary cancer or an unexpected metastasis when an abnormal finding indicative of a second primary cancer is obtained on ^{18}F-FDG PET/CT. Most second primary cancers detected by PET/CT (83.3%, 20/24) were in the early stage (I, II), which might provide a better opportunity for cure. During a follow-up of 9.2±5.2 months, no second primary cancers were found except for 1 case with an early gastric cancer that was detected incidentally by endoscopy. This emphasizes the value of ^{18}F-FDG PET/CT in detecting a second primary cancer. In addition, this study demonstrates that ^{18}F-FDG PET/CT is superior to conventional staging work-up to screen a synchronous second primary cancer due to the significantly higher sensitivity. In this study, the PET/CT fusion images provided additional information in 22 (48.9%) out of 45 lesions with an abnormal focal FDG uptake that was indicative of a second primary malignancy with an accurate anatomic localization and a concurrent anatomical abnormality. This shows that PET/CT is more suitable for screening a second primary cancer than conventional PET. Figure 1 shows a typical case demonstrating the value of fused PET/CT images. When only the PET images were reviewed, it was difficult to differentiate the physiological uptake from a pathological lesion in the sigmoid colon. The CT and fused PET/CT images showed localized wall thickening in the sigmoid colon, which suggests a second primary sigmoid colon cancer.

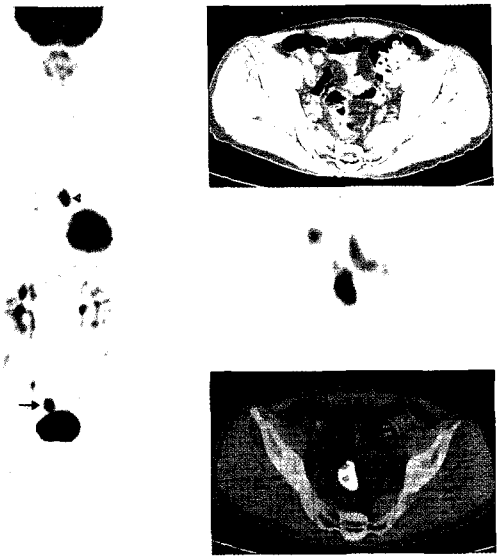

Fig. 1. ^{18}F-FDG PET/CT image of a 73-year-old male patient with an esophageal squamous cell carcinoma showing a hypermetabolic mass in the sigmoid colon (arrow, maximum standardized uptake value=13.9) along with focally increased uptake in the mid thoracic esophagus (arrowhead, maximum standardized uptake value=13.1), which was found to be an adenocarcinoma by an endoscopic biopsy.

Table 1. Summary of the Literature Dealing with the Use of PET in Evaluating a Second Primary Cancer

Authors	Modality	Subjects No.	Index tumor	SPC and/or M1	Sensitivity of CSW	PET*		Notes
						Sensitivity	PPV	
Keyes, et al.[12]	PET	66	Head and neck cancer	4.5% (3/66; all SPCs)	66.7% (2/3)	100% (3/3)	100% (3/3)	Not whole body scan protocol †No pathological confirmations in 7 patients with abnormal PET findings
Stokkel, et al.[13]	PET	68	Head and neck cancer	17.6% (12/68, all SPCs)	41.7% (5/12)	100% (12/12)	100% (12/12)	Not whole body scan protocol
Stuckensen, et al.[14]	PET	106	Head and neck cancer	9.4% (10/106; SPCs in 3, M1 in 7)	0%	100% (10/10)	NA	Not mention PPV of PET
Nishiyama, et al.[15]	PET	53	Head and neck cancer	15.1% (8/53; SPCs in 6, M1 in 2)	50.0% (4/8)	87.5% (7/8)	70.0% (7/10)	False negative in 1 prostate cancer
Reed, et al.[16]	PET	287	Lung cancer	6.3% (18/287; SPCs in 3, M1 in 15)	0%	100% (18/18)	48.6% (18/37)	†No further diagnostic confirmations in 8 patients with abnormal PET findings
Liberale, et al.[17]	PET	58	Esophageal cancer	13.8% (8/58; SPCs in 1, M1 in 6, and both SPC and M1 in 1)	0%	100% (8/8)	61.5% (8/13)	
Van Westreenen, et al.[18]	PET	366	Esophageal cancer	2.7% (10/366; all SPCs)	50% (5/10)	100% (10/10)	50.0% (10/20)	
Agress, et al.[19]	PET	1,750	Various	0.7% (12/1750; all SPCs)	0%	100% (12/12)	28.6% (12/42)	Unclear description of the index tumors† No further diagnostic confirmations in 16 patients with abnormal PET findings
Schmid, et al.[21]	PET/CT	48	Head and neck cancer	6.3% (3/48; SPC in 1, M1 in 2)	0%	100% (3/3)	50.0% (3/6)	
Goerres, et al.[22]	PET/CT or PET	26	Treated head and neck cancer	11.5% (3/26; SPC in 1, M1 in 2)	0%	100% (3/3)	100% (3/3)	
Ishimori, et al.[23]	PET/CT	1,912	Various	1.2% (22/1912; all SPCs)	0%	100% (22/22)	55.0% (22/40)	Unclear description of the index tumors† No further diagnostic confirmations in 39 patients with abnormal PET findings
Choi, et al.[24]	PET/CT	547	Various	6.0% (34/547; SPCs in 26, M1 in 7)	50.0% (17/34)	91.2% (31/34)	68.9% (31/45)	False negative in 3 gastric cancers PET/CT fusion images provided additional information in 48.9% on a lesion by lesion basis. †No further diagnostic confirmations in 8 patients with abnormal PET findings
Summary		5,287		2.7% (143/5,287; SPCs in 101, M1 in 42)	23.1% (33/143)	97.2% (139/143)	55.8% (129/231)	

SPC: second primary cancer, CSW: conventional staging work up, PPV: positive predictive value, NA: not available
* The sensitivity and PPV of CSW and PET were obtained for second primary cancer and/or distant metastasis.
†Cases with abnormal PET findings where no further diagnostic confirmations were excluded from the calculations of the sensitivity and PPV.

Discussion

Table 1 summarizes the recent literature of ^{18}F-FDG PET/CT or PET in evaluating a second primary cancer. The overall incidence of a synchronous second primary cancer was 1.9% (101/5,287) on a patient-by-patient basis. There were 103 synchronous second primary cancers in 101 patients. The most common sites of second primary cancers were the lung (22.3%), head and neck (17.5%), colon and rectum (15.5%), thyroid (14.6%), stomach (7.8%), genitor-urinary organ (7.8%), esophagus (4.9%), and others (9.7%). PET showed an excellent sensitivity of 97.2% and a modest positive predictive value of 55.8% for detecting a synchronous second primary cancer or M1 disease. In

contrast, conventional staging work-up showed a sensitivity of 23.1%. This demonstrates ^{18}F-FDG PET/CT or PET to be more sensitive than conventional staging work-up to find a second primary cancer or M1 disease. The positive predictive value of PET/CT (62.8%, 59/94) for detecting a synchronous second primary cancer or M1 disease appears to be higher than that of conventional PET based on the literature (51.1%, 70/137; p=0.08 by Fisher's exact test). Currently, whole body ^{18}F-FDG PET/CT is the best non-invasive diagnostic modality for screening a synchronous second primary cancer. Therefore, when abnormal findings indicative of a second primary cancer are found on PET/CT, a further diagnostic work-up will be essential to rule out the presence of a second primary cancer and/or an unexpected metastasis. PET/CT is more suited to detecting a second primary tumor than conventional PET by providing both metabolic and anatomical information and by having a better positive predictive value.

From the literature of PET, there were 102 false positive sites for second primary cancer or M1 disease indicated by PET/CT or PET. The frequent false positive sites are as follows: colon and rectum (39.2%), thyroid (18.6%), brain (7.9%), lung (5.9%), head and neck (5.9%), liver (3.9%), esophagus (2.9%), and others (15.7%). When focal ^{18}F-FDG uptake is observed in the colon, rectum or thyroid, it is difficult to differentiate a malignancy from benign or physiological lesions using the degree of ^{18}F-FDG uptake such as a standardized uptake value alone due to significant overlap in values.[25,26] In colororectal lesions with a focal ^{18}F-FDG uptake, PET/CT cannot provide an accurate differential diagnosis between malignant and benign or physiological uptake.[25] For thyroid lesions, it was recently suggested that image interpretation that included the ^{18}F-FDG uptake and the CT attenuation pattern, along with the standardized uptake value, significantly improved the accuracy of PET/CT in differentiating benign focal thyroid lesions from malignant focal thyroid lesions.[26] However, further study will be needed.

In conclusion, whole body ^{18}F-FDG PET/CT is useful for screening second primary cancers with a high sensitivity and good positive predictive value. In order to rule out the presence of a second primary cancer or an unexpected metastasis, further diagnostic work-up is essential when abnormal findings indicative of a second primary cancer are found on the PET/CT images. PET/CT is better in detecting a second primary tumor than conventional PET.

요 약

이 종설은 이차성 원발암에서의 ^{18}F-FDG PET/CT의 이용을 다루었다. 암환자에서 이차성 원발암의 발병 유무는 주요한 예후인자 중의 하나이다. 이차성 원발암을 조기에 진단하고 치료하는 것은 이와 관련된 암 사망률을 낮추는 데 중요하다. ^{18}F-FDG PET/CT는 해부학적 및 대사적 정보를 동시에 제공함으로써 종양 영역에서 CT나 기존의 PET보다 진단성능이 더 우수하다. 이러한 우수한 진단성능과 전신영상이 가능하다는 장점 때문에 PET/CT는 이차성 원발암을 발견하는 데에 CT나 기존의 PET보다 더 적합하다. ^{18}F-FDG PET/CT는 이차성 원발암에 대한 선별검사로서 높은 예민도와 비교적 좋은 양성예측도를 보이므로 유용하다. PET/CT 영상에서 이차성 원발암이 의심되는 병변이 보일 경우 추가적인 진단적 검사는 필수적이다. PET/CT는 이차성 원발암을 발견하는데 PET보다 우수하다.

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