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Original

Preoperative Diagnosis of Multiple Primary Malignant Neoplasm in Gastrointestinal and Breast Cancers : Impact of FDG-PET/CT

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SUMMARY

Objective : The reports of multiple primary malignant neoplasm (MPMN) have increased due to the development of imaging technologies that have influenced the extension of the 5-year relative survival rate for all cancers. Integrated positron emission and computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) has shown its advantages for detecting, staging, evaluating the prognosis, and offering better insights for survivors, their families and physicians. The aim of this study was to retrospectively investigate the impact of whole-body FDG-PET/CT in detecting MPMN during the initial staging work-up of gastrointestinal and breast malignancy, and to describe their characteristics.

Methods : The cases were identified by reviewing the Dokkyo Medical University Hospital PET Center's database, searching for patients referred from the Department of Surgical Oncology and the Department of Gastroenterological Surgery, who underwent preoperative staging with whole-body FDG PET/CT at our center between January 2007 and December 2009. A total of 778 patients matched these criteria. Of them, 40 PET/CT reports mentioned suspicious cases of MPMN. The medical records of these 40 cases were retrieved and examined. The follow-up data of these patients was reviewed until February 2010.

Results : Of 778, 32 patients were diagnosed with additional unexpected cancers, which 27 (3.5%) were incidental double cancers and 5 (0.64%) had triple primary lesions. Overall 37 MPMN, twelve corresponded to stage 0, nineteen to stages I－II, three to stages III－IV, and three remained uncertain. Sensitivity and positive predictive value of FDG PET/CT in detecting a controversial lesion were 76.5% and 70.3%, respectively. The colorectum was the most common site for synchronous MPMN (17 of 37 cancers ; 45.9%), followed by stomach (9 ; 24.3%), prostate (3 ; 8.1%), thyroid (3 ; 8.1%), breast (2 ; 5.4%), biliary duct (1 ; 2.7%), kidney (1 ; 2.7%), and lung (1 ; 2.7%).

Conclusions : FDG PET/CT was useful for finding multiple primary malignant neoplasm with a relatively high sensitivity. Physicians should pay special attention to rule out the presence of unexpected additional primary lesions in initial staging work-up for colorectal cancer.

Key Words : PET/CT, FDG, multiple primary malignant neoplasm, synchronous cancer

INTRODUCTION

Cancer is a leading cause of death worldwide. It accounted for 12.7 million new cases and 7.6 million deaths in 2008[1)]. While human life expectancy is in-

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creasing in recent years, cancer incidence may be expected to increase to 27 million new cases by the year 2030[2] It is also reasonable to assume that synchronous cancers, multiple primary malignant neoplasm (MPMN) occurring simultaneously, may no longer be a rare medical incidental curiosity, but may become a great threat ; one worthy of study not only because of its own significance but also because it offers many directions of approach to the overall study of neoplasm. In 2009, the American Cancer Society highlighted the increased number of new cases of MPMN due to the development of screening tests that has influenced the extension of the 5-year relative survival rate for all cancers combined from 50% in 1975-1977 to 66% in 1996-2004[3]. In this scenario, ageing societies, such as Japan[4], should be aware of this increasing menace.

Integrated positron emission and computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) is a novel clinical imaging modality that has shown throughout the last decade its advantages for detecting, staging, evaluating the prognosis of various tumors, and offering better insights for survivors and their families and physicians[5~7].

The objective of this study was to retrospectively investigate the impact of whole-body FDG-PET/CT in detecting MPMN during the initial staging work-up of gastrointestinal and breast malignancy, and to describe their characteristics.

METHODS

Study design and site

This was a descriptive-retrospective study conducted at the Dokkyo Medical University Hospital PET Center (DMUH-PET Center), a quaternary referral care center affiliated to the tertiary referral care 1,167-bed university hospital of Dokkyo Medical University in Mibu, Tochigi, Japan. The DMUH-PET Center was established in 2005, as the first PET/CT provider in the northern Kanto region, which embraces the Gunma, Ibaraki and Tochigi prefectures. The DMUH-PET Center annually performs a mean of 3,600 examinations, mainly for oncological purpose.

Participants

The cases were cancer patients, who, during the preoperative staging with whole-body FDG PET/CT for a histopathological proven primary malignant neoplasm (index lesion), incidentally had another cancer. Multiple primary malignant neoplasm diagnosis and their histological and topographic classification were done according to the International Rules for Multiple Primary Cancers[8]. Although no consensus was present on synchronous and metachronous tumor definition, in the current study were defined as follows : synchronous cancers were second primary malignant neoplasm occurring within 6 months of the diagnosis of the first primary cancer, whereas metachronous cancer were defined as those that were diagnosed after an interval of $>$ 6 months.

The cases were identified by reviewing the DMUH-PET Center's database, searching for patients referred from the Department of Surgical Oncology and the Department of Gastroenterological Surgery, who underwent preoperative staging of gastrointestinal and breast malignancy with whole-body FDG PET/CT at our center between January 2007 and December 2009. A total of 778 patients matched these criteria. Of them, 40 PET/CT reports mentioned suspicious cases of MPMN. The medical records of these 40 cases were retrieved and examined. The follow-up data of these patients was reviewed until February 2010.

Data collection

Data was collected between October 2009 and February 2010 from the DMUH-PET Center's electronic database and the patients' clinical records from the hospital electronic database. Using a record sheet designed for the objectives of this study, we collected demographic characteristics (age, sex), risk factors for cancer, such as body mass index (BMI), tobacco smoking, alcohol drinking, history of cancer in first-degree family members and presence of diabetes mellitus, arterial hypertension and/or personal oncological history.

Data collected on the index primary malignant neoplasm and additional synchronous cancers included : site and size, PET/CT TNM staging, histopathology and pathological staging, treatment, occurrence of relapse and/or metastases and standardized uptake value (SUV). SUV is defined as the retention of FDG normalized to an injected dose and patient body weight. It is an established index for quantifying glucose metabolic activity in tissues. For this study, an increased

Table 1 Demographic characteristics and risk factors of 32 patients with MPMN

Age (years)	71.1 ± 10.5
Sex (M/F)	19/13
History of cancer in first-degree family members	9 (28.1%)
One relative with cancer	4 (12.5%)
Two or more relatives w/cancer	5 (15.6%)
Habitual smoking	15 (46.9%)
Male	11 (34.4%)
Female	4 (12.5%)
Pack Year*	30.6 ± 22.6
Habitual alcohol intake	8 (25.0%)
Male	6 (18.8%)
Female	2 (6.3%)
Gram of ethanol/week	19.9 ± 17.1
Diabetes Mellitus	7 (21.9%)
Body mass index	21.8 ± 3.5
Underweight	6 (18.8%)
Normal	20 (62.5%)
Overweight	4 (12.5%)
Obesity	2 (6.3%)
Arterial Hypertension	14 (43.8%)
Patients' Previous Oncological History	1 (3.1%)†

Abbreviations : MPMN, multiple primary malignant neoplasm

* Pack Year = number of packs times years reported. 1 pack = 20 cigarettes

† Patient had a previous breast cancer ten years before the present study.

uptake with a maximum SUV (SUVmax) greater than 3.0 was considered as a suspicious lesion for neoplasm that required further examination[9].

Statistical analysis

Data analysis was performed using SPSS for Windows version 16. Descriptive analysis was performed for the studied variables. Frequencies were determined for all categorical variables, while mean and standard deviation was calculated for continuous variables. Sensitivity and positive predictive value of PET/CT to detect MPMN was calculated.

RESULTS

From the 40 PET/CT that were reported as suspicious of MPMN, eight were not confirmed as MPMN with the pathologic study : six benign tumors (located in the thyroid, colon, breast, pancreas, lung), a liver metastasis, and one without pathological diagnosis. These resulted in a sensitivity of 76.5% and a positive predictive value (PPV) of 70.3% . Of 778, 32 patients (4.1%) were diagnosed with additional unexpected cancers, which 27 (3.5%) were incidental double cancers and 5 (0.6%) had triple primary lesions ; giving a total of 37 synchronous malignant lesions.

Table 1 shows the demographic characteristics and some of the known risk factors for cancer of the 32 investigated cases (male = 19 ; female = 13). The mean age of the cases was 71.1 ± 10.5 years ; and the age range between 71 and 80 years was the most prevalent (56.3% ; 13 males and 5 females).

History of cancer in first-degree family members was observed in nine of the patients (28.1%), from which 55.6% had 2 or more relatives with cancer. Risky habits were mainly present in males, 34.4% of whom were smokers, 18.8% drinkers, and 15.6% both smokers and drinkers. Excluding 6 patients without addictive behavior records, 25.0% consumed alcohol, with a mean of 19.9 ± 17.1 g of ethanol per week. Of the six patients (18.8%) with BMI ≥ 25, four were

Table 2 Description of the 32 patients with double or triple primary cancer

			Index Primary Cancer					Second Primary Cancer					Third Primary Cancer				
No	Age	Sex	Site	Patho	Stage	SUV_{max}	Out come	Site	Patho	Stage	SUV_{max}	Out come	Site	Patho	Stage	SUV_{max}	Out come
6	70	MAL	CRC	POR	I	14.98	OUT	CRC	WEL	0	10.22	NRM	PRO	POR	I	8.75	NRM
7	50	FEM	CRC	MOD	III A	16.1	OUT	CRC	MUC	III B	11.3	OUT	CRC	MOD	0	7.5	NRM
8	77	MAL	CRC	POR	III A	12.4	NRM	CRC	WEL	0	9.4	NRM	CRC	MOD	0	9.1	NRM
24	60	MAL	CRC	MOD	IV	12.4	OUT	STO	MOD	0	10	NRM	CRC	POR	I	10	NRM
31	71	FEM	CRC	WEL	II	16.24	OUT	STO	WEL	I A		NRM	CRC	MOD	0		NRM
3	73	FEM	CRC	MOD	II	16.3	NRM	CRC	WEL	0		NRM					
4	75	MAL	CRC	WEL	I B	8.3	NRM	CRC	WEL	0	11.4	NRM					
5	62	MAL	CRC	WEL	III B	9.3	DEC	KID	No data	IV	11.3	UNO					
9	79	MAL	CRC	WEL	II	21.39	OUT	STO	WEL	I A		NRM					
10	83	FEM	CRC	MOD	III A	23.5	DEC	THY	No data	No data	9.6	OPE					
11	65	MAL	CRC	MOD	II	16.08	OUT	CRC	WEL	I	4.5	NRM					
12	81	FEM	CRC	MOD	III A	30.02	OUT	CRC	MUC	I	4.74	NRM					
14	85	FEM	CRC	MOD	II	13.53	NRM	CRC	POR	I	8.19	NRM					
15	78	FEM	CRC	WEL	IV	13.8	OUT	CRC	WEL	I	6.9	NRM					
16	84	FEM	CRC	POR	III A	9.4	NRM	STO	MOD	I B	35.4	NRM					
17	80	MAL	CRC	POR	I	10.2	NRM	CRC	POR	I	3.7	NRM					
18	68	FEM	CRC	MOD	I B	14.5	NRM	THY	No data	No data	2	NRM					
19	71	MAL	CRC	MOD	IV	45	REF	PRO	No data	IV	40	UNO					
21	74	MAL	CRC	MOD	I	2.79	NRM	LUN	MUC	I	9.63	NRM					
22	75	MAL	CRC	POR	III A	18.1	NRM	STO	MUC	I A	4	NRM					
23	79	MAL	CRC	POR	II	12.3	NRM	STO	MOD	I A		NRM					
25	41	MAL	CRC	MOD	II	15.65	NRM	CRC	POR	0	11	NRM					
26	71	FEM	CRC	MOD	II	12.35	NRM	STO	MOD	I A		NRM					
27	75	MAL	CRC	MOD	III B	15.2	NRM	CRC	WEL	I		NRM					
29	76	MAL	CRC	MOD	II	14.55	OUT	STO	WEL	0		NRM					
30	77	MAL	CRC	WEL	IV	43.51	OUT	STO	WEL	0		NRM					
32	66	MAL	CRC	WEL	IV	10.26	OUT	PRO	No data	No data		UNO					
1	45	FEM	BRE	SCI	IV	9.6	OUT	BRE	SOL	II B	6	NRM					
2	74	FEM	BRE	PAP	II A	7.95	OUT	THY	FOL	II	18.45	NRM					
20	61	FEM	BRE	PAP	I	1.5	NRM	BRE	PAP	I	3.1	NRM					
13	75	MAL	STO	WEL	I A	4.87	NRM	BIL	CHO	0		NRM					
28	73	MAL	DUO	MOD	II	4.05	OUT	CRC	POR	I	6.1	NRM					

Abbreviation. FEM : Female ; MAL : Male ; Patho : Pathology ; SUVmax : maximum standardized uptake value

[Site] BIL : Biliary ; BRE : Breast ; CRC : Colorectum ; DUO : Duodenum ; KID : Kidney ; LUN : Lung ; PRO : Prostate ; STO : Stomach ; THY : Thyroid

[Outcome] NRM : No evidence of recurrence or metastasis by the end of the follow-up period of this study ; DEC : Deceased ; OPE : Operated ; OUT : Outpatient* ; REF : Referred ; RT : Radiotherapy ; UNO : Unoperable.

[Histopathology] CHO : Cholangiocarcinoma ; FOL : Follicular variant of papillary thyroid carcinoma ; MOD : Moderately differentiated adenocarcinoma ; MUC : Mucinous Adenocarcinoma ; PAP : Papillotubular Invasive Ductal Carcinoma ; POR : Poorly differentiated adenocarcinoma ; SOL : Solid-tubular Invasive Ductal Carcinoma ; SCI : Scirrhous Invasive Ductal Carcinoma ; WEL : Well-differentiated adenocarcinoma.

*Outpatient check-up according to follow-up guidelines after finishing treatment

women with a total of three thyroid, two breast, and two colon primary cancer lesions. Among the two men with BMI ≥ 25, a total of four colorectal cancer lesions were diagnosed. On the contrary, of the six patients with underweight, a total of eight colon, three gastric, and a renal primary cancer lesions were found.

Table 2 describes the thirty-two patients and the characteristics of their thirty-seven lesions. Of the 32 patients, 27 had double and 5 triple cancers. From a total of 37 MPMN, 17 colorectal lesions (45.9%) were the most common frequent, followed by stomach (9 ; 24.3%), prostate (3 ; 8.1%), thyroid (3 ; 8.1%), breast (2 ; 5.4%), biliary duct (1 ; 2.7%), kidney (1 ; 2.7%), and lung (1 ; 2.7%). For the index cancer, SUVmax ranged between 1.5 and 45 ; and for the synchronous cancers, the SUV max ranged between 2 and 40. Within the MPMN found, 32.4% corresponded to stage 0, 78.4% were at stages 0－I, and 91.9% at stages 0, I, II. Moreover, 86.5% were curatively resected.

DISCUSSION

Currently, there is an increasing need to find the optimal screening modalities and strategies to reduce mortality from second malignancies[10] ; we believe that FDG PET/CT may play an important role as a reliable alternative for MPMN screening. In our study, FDG PET/CT was effective in finding 37 incidental primary lesions with a sensitivity of 76.5% and a PPV of 70.3% . Of them, 91.9% were in early stage (0－II) and 86.5% were curatively resected. Other studies also agreed about the important role of preoperative staging with FDG PET/CT for MPMN evaluation and treatment[11~14]. In these studies, sensitivity and PPV rates were between 88% －100% and 59% －93.7%, respectively. As in our study, most synchronous cancers were detected at an early stage with successful resection rates.

In 1991, the National Cancer Center Hospital (Tsukiji, Tokyo, Japan) reported a MPMN prevalence of 4.0% and noted an increase from 3% in 1962[15]. With PET/CT, we found a prevalence of 4.1% (32 of 778 patients), which contrasted with a compendious literature review about MPMN prevalence diagnosed by PET/CT (Table 3-1)[11,16,17], as well with the detection rate of primary cancer in healthy asymptomatic individuals during cancer screening with whole-body PET/CT (Table 3-2)[18~26]. In Western countries' studies, a literature review reported a prevalence of MPMN between 0.73% and 11.7%[27].

Although patients in our study showed an age range between 41 and 85 years, majority of them (69%) were older than 70 years. Previous studies have also described a higher prevalence of MPMN among this age bracket[28,29], and it is a criterion that should be taken into consideration for performing PET/CT during the initial staging and/or follow-up planning.

Alcohol drinking and tobacco smoking have been previously described as risk factors for MPMN[3,11,30,31]. In our study, although there were no statistically predominant risk factors, there was a tendency to tobacco smoking (46.9%), history of cancer in first-degree family member (28.1%) and alcohol drinking (25.0%) in patients with MPMN. A recent study of the impact of tobacco smoking on the subsequent risk of cancer in Japan, showed an overall frequency of smoking of 53.9 % (men 83% , women 8.9%) in patients who developed cancer[32]. This dramatically contrasts with our results, which show a lower frequency for men (57.9 %) and a much higher frequency for women (30.8%). These results may suggest a stronger relation between tobacco smoking and MPMN in women, which deserves further study, as possible associations can give additional insights into which patients should receive PET/CT screening.

Of all 37 MPMN, eleven (29.7%) had a SUVmax < 3.0, with a mean tumor size of 14 mm (2–30 mm). Of them, nine lesions were bigger than 10 mm : five were located in the stomach, two in the colon, one in the thyroid and another in the prostate. These sites have particularly increased physiological FDG uptake[33], hindering the visualization of possible local malignant lesions. Moreover, some neoplasms are non-FDG-avid, such as low-grade tumors, mucinous and neuroendocrine tumors, renal cell carcinoma, and certain types of lymphoma[34]. Therefore, if a tumor is suspected by the morphological component of PET/CT examination, further specific screening test should be considered. In addition, dual-time FDG PET/CT imaging, meaning an early and delayed phase scan, may give extra details about the local metabolism allowing a better approach to suspicious FDG accumulations[35].

In this study, MPMN of the gastrointestinal tract

Table 3-1 Literature review for prevalence of MPMN detected by PET/CT.

Country	Author	Total no. of patients with cancer	No. of patients with MPMN	%	Most frequent MPMN
Japan	Suzuki (2008)[a]	43	1	2.3%	ESO
Japan	Takekawa (2007)[b]	964	11	1.1%	BIL, CRC, HEP, LUN, PRO, STO, THY
Korea	Choi (2005)[c]	547	26	4.8%	LUN, STO

Information from abstracts found in Pubmed under MeSH keywords : ["Positron-Emission Tomography" AND "Neoplasms, Multiple Primary"]. Cited 2010 Oct.
Abbreviation. MPMN : Multiple primary malignant neoplasm ; UGI : upper gastrointestinal
[Site] BIL : Biliary ; CRC : Colorectum ; ESO : Esophagus ; HEP : Liver ; LUN : Lung ; PRO : Prostate ; STO : Stomach ; THY : Thyroid
a. Aim to analyze the sensitivity of FDG-PET and FDG-PET/CT to detect upper gastrointestinal MPMN.
b. Report of MPMN found by PET/CT
c. Patients underwent PET/CT staging or restaging due to suspicion of primary cancer of UGI tract.

Table 3-1 Literature review for prevalence of primary tumors detected by PET/CT screening.

Country	Author	Total no. of asyntomatic individuals	No. of individuals with cancer	%	Most frequent site
Japan	Ide (2006)[a]	9,357	296	3.2%	CRC, LUN
Japan	Nishizawa (2009)[a]	1,197	18	1.5%	THY
Korea	Lee (2009)[a]	1,336	16	1.2%	THY
Japan	Terauchi (2008)[a]	2911	28	1.0%	CRC
Japan	Minamimoto (2007)[a]	50,558	395	0.8%	CRC, THY
Japan	Kaida (2008)[a]	660	5	0.8%	BRE
Japan	Kojima (2007)[b]	4881	36	0.7%	THY
Japan	Ghotbi (2007)[c]	Not stated	Not stated	0.5%	Not stated
Japan	Shoda (2007)[d]	2861	2	0.1%	STO

Information from abstracts found in Pubmed under MeSH keywords : ["Positron-Emission Tomography" and screening]. Cited 2010 Oct.
Abbreviation. [Site] BRE : Breast ; CRC : Colorectum ; LUN : Lung ; STO : Stomach ; THY : Thyroid
a. Cancer screening with whole-body PET/CT for healthy asymptomatic individuals.
b. Historical cohort study to evaluate the diagnostic performance of cancer screening using whole-body FDG-PET.
c. Cancer screening with whole-body PET/CT for healthy asymptomatic Japanese.
d. FDG-PET screening for upper gastrointestinal cancers compared with endoscopic diagnosis as the gold standard.

were the most frequent (73.0% ; seventeen colorectal and ten gastric of 37 cancers). Of the 17 synchronous colorectal cancer (CRC), 16 (94%) were at stage 0-I, which were successfully treated. These clinical characteristics and pathological findings were similar to the colorectal synchronous lesions described in a prospective study[36]. A predisposition for multiple primary colorectal carcinomas in patients with longstanding ulcerative colitis (18%) and familial adenomatous polyposis (21%) is well known[37], however in our cases there was no familial genetic component.

CRC was the most common within the 5 triple cancer patients. Whole-body PET/CT for tumor staging has increased the detection rate of unexpected synchronous cancers. Although odds of having more than two synchronous primary neoplasms are small, PET/CT may increase the prevalence[38].

Regarding the SUVmax for colorectal MPMN in this study, the mean SUVmax = 6.7 ± 3.9 was comparable to those MPMN found by PET/CT colonography[39]. The superimposition of the precise structural findings provided by CT to a hypermetabolic focus seen at PET

makes PET/CT a powerful cancer diagnostic tool. Furthermore, SUVmax adds another advantage for PET/CT semi-quantifying the local accumulation of FDG, which may elucidate MPMN aggressiveness diagnosis, tumor response to treatment, and relapse screening[9].

In conclusion, preoperative FDG PET/CT staging is useful for screening a second primary cancer with a high sensitivity and positive predictive value. Yet complementary diagnostic work-up is essential to rule out the presence of MPMN and to plan the therapeutic strategy. In addition, as MPMN might be detected at early stages of the disease, prognosis and survival may be favorable. Finally, physiological increase of FDG uptake should not be taken carelessly, especially in sites particularly rare to be a benign lesion or metastatic spreading, and the possibility of MPMN should be considered.

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Conflicts of interest

There are no conflicts of interests regarding this study.

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