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Impact of FDG PET/CT on detection of synchronous and metachronous malignancies and clinical management in patients with multiple primary cancers

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Multiple primary cancers are usually defined as primary malignant tumors of different histological origins in one person. Recently, there has been an increase in the number of patients diagnosed with multiple primary cancers. The study aims to evaluate the role of PET/CT in detecting second primary and subsequent tumors as well as to demonstrate the influence on the treatment management in patients with histologically proven synchronous or metachronous tumors. Fifty patients with clinically proven at least one malignancy have been evaluated and followed up for a year. Another inclusion criterion was a biopsy-proven additional primary synchronous (within 2-6 months after the first one) or metachronous (more than 6 months after the diagnosis of the first one) malignant tumor in a different organ. All patients were scanned on GE Discovery PET/CT 16 slices scanner from the top of the head to mid-thigh. The study was performed one hour after injection, using the weight-adjusted activity, hydration of patients with diuretic stimulation, and oral/i.v. contrast intake. Thirty out of 50 patients were females. The youngest patient was 25 years old, while the highest age was 84 years. Ten of the patients had third primary tumors and one patient had four different malignancies. Metachronous tumors were 2.4-fold higher than synchronous ones. The minimum time to detect a second tumor was 1 month, while the maximum was 15 years. As second malignancies we detected fourteen gastrointestinal cancers (28%), ten urogenital ones (20%), ten pulmonary tumors (20%), five breast cancers (10%), four lymphoma patients (8%), four head and neck squamous cell carcinomas (8%), two NET (4%), and one sarcoma (2%). As a result of the 18F-FDG PET/CT scan, the therapy plans of all 50 patients required modification at the minimum for the second tumor. 64% of the patients had multimodality therapy for their first cancer, which suggests that this approach could play an important role in the development of MPM. 81% of the additional malignancies in the female group, detected by PET/CT were in stages I or II, which provides a higher probability of cure. On the other hand, we detected advanced stage second primary disease in 70% of the patients in the male group. PET/CT can identify a significant number of additional primary neoplasms in patients with known primary cancer, acquiring combined metabolic and morphologic information, as well as its whole-body protocol. Integrated PET/CT can significantly modify the assessment of the tumor's dissemination and often change patient management substantially. Subsequent primary lesions identified after PET/CT scan are mainly in the early stage and thus have an excellent likelihood of being cured if treated promptly and aggressively.

Key words: multiple primary cancers; 18F-FDG PET/CT; detection; treatment management

Multiple primary cancers (MPM) are usually defined as primary malignancies of different histological origins in one person. They may be limited to a single organ or involve two or more completely separate anatomical structures [1]. Multiple primary cancers can be classified into two main categories based on the interval between the diagnoses: synchronous cancers are tumors occurring simultaneously or within 6 months after the first one, while metachronous multiple malignancies develop more than 6 months after the first neoplasm, according to the International Agency for Research rules (IARC rules) [2].

According to Warren Gates criteria, a diagnosis of MPM includes the following requirements to be fulfilled: each tumor should present a definite picture of malignancy; each tumor should be histologically distinct; the possibility that one of the tumors is a metastasis of the other must be excluded [3].

Over the last two decades, 18F-FDG whole-body PET has been used successfully and more frequently for the evaluation and clinical management of an expanding number of neoplasms [4–7]. Reports also indicate that the method is more accurate than CT in identifying unexpected metastatic

foci and recurrent tumors that were either not seen or were difficult to be detected on CT scans [8–10]. Moreover, a routine interpretation of 18F-FDG PET findings can identify incidental foci of hypermetabolism that are unlikely to be related to the neoplasm that prompted the scan [10–12]. Combined PET/CT has recently emerged as a promising hybrid imaging modality and shortly can be used routinely in clinical situations with synchronous and metachronous multiple primary tumors [13–15]. The present study retrospectively evaluates the yield of whole-body 18F-FDG PET/CT for the detection of unexpected additional primary cancers in patients with known malignancies.

Patients and methods

Patients. The cases included in this study were patients at the Nuclear Medicine Department in Alexandrovska Hospital having a biopsy-proven first primary tumor. From September 2018 to August 2019 (12 months); 3,500 patients were referred to our institute for a whole-body FDG PET/CT scan. A second inclusion criterion was a biopsy-proven second or third primary synchronous (within 2–6 months after the first one) or metachronous (more than 6 months after the diagnosis of the first one) malignant tumor in a different organ. The cases of biopsy-proven synchronous or metachronous tumors (the second or third primary tumor) seen at our department during the aforesaid period were 50. There was a total of 20 male and 30 female cases, with a male to female ratio of 1:1.5. The youngest patient was 25 years old while the highest age observed was 84 years, with a mean age of 62.6 years. The follow-up duration of these cases was 24 months counting from the time of diagnosis of the second tumor. The minimum time to detect a second tumor was 1 month while the maximum was 15 years. The number of synchronous tumors was 12 – 8 in males and 4 in females.

18F-FDG PET/CT technique. All patients underwent 18F-FDG PET/CT imaging after at least 6–8 h of fasting. Before injection of 18F-FDG, the medical history, weight, and serum glucose level of each patient were recorded. A serum glucose level <10 mmol/l was an obligatory prerequisite for performing the procedure. Whole-body PET scanning from the skull base to the upper thighs was performed (using GE Discovery 600 PET/CT scanner) approximately one hour after the intravenous injection of 3–3.5 MBq/kg of 18F-FDG. CT component is performed by a multidetector CT scanner and the following parameters: auto mAs (50–120); 120 kV, 2.5 mm slice thickness. Then the PET data were collected in the reverse direction immediately after CT acquisition with a time of 2–4 minutes/bed position. All patients received an oral contrast and some of them received an intravenous contrast as well. When an intravenous contrast was administrated, the CT parameters were 50–340 mAs and 120 kV. A total volume of 100 ml of the IV contrast agent (Ultravist) was injected using a power injector at a flow rate of 2–3 ml/s.

Image reconstruction and interpretation. Image readout was conducted on an AW4.5 WorkStation (GE Healthcare), which allowed visualization of PET, CT, and fused sections in transverse, coronal, and sagittal planes Maximum standardized uptake values were automatically generated by the software. Two experienced nuclear medicine specialists reviewed the study independently. When the intravenous contrast was administered, the images were evaluated alongside a radiology specialist. Lesions were recognized as abnormal foci of elevated tracer uptake relative to that of surrounding tissues and normal comparable contralateral structures. If lesions presented any signs of malignancy on CT, they were also considered malignant, even if these were non-avid on PET (SUVmax <2.5).

Data analysis. A PET/CT finding was considered positive when the diagnosis was confirmed histologically in a sample from the suggested site/sites of probable second/third primary tumor taken through.

Image evaluation and analysis were performed retrospectively. The data was collected and analyzed concerning age, gender, location of the first primary tumor; location of the second or subsequent synchronous or metachronous tumor, the time elapsed between the two tumors' detection, the treatment received for both tumors, and the outcome. The results were presented in form of tables, figures, or in a descriptive manner. All data were tabulated and analyzed in a Microsoft Excel spreadsheet.

Results

The first primary malignancy in the majority was breast cancer in females (21 of 30 female patients, 70%) and gastrointestinal cancer (GIT) in males (10 of 20 male patients, 50%). Lung (4 of 12 cases) and GIT (4 of 12 cases) cancers are the commonest synchronous tumor while urogenital cancers (UGC) and colon cancers are the commonest site of the metachronous tumor (each group of 8 cases), independent of the first primary tumor. As second malignancies, we located fourteen GIT cancers (14p, 28%), ten UGC ones (10p, 20%), ten pulmonary tumors (10p, 20%), five breast cancers (5p, 10%), four lymphoma patients (4p, 8%), four head and neck squamous cell carcinomas (4p, 8%) two NET (2p, 4%), and one sarcoma (1p, 2%). Details regarding age, sex, the first primary tumor, time elapsed between the two tumors, type of the second tumor, stages of both malignancies, and outcome, are described in Table 1 and Table 2. The relationship between the 1st primary, 2nd synchronous, and 2nd metachronous tumors is shown in Figure 1.

The incidence of patients with three primary malignancies in the group was 20% (10 cases) respectively: four patients with breast cancers, three patients with prostate cancers, two patients with lymphoma, and one with bladder cancer, were treated in the past. One patient in our study (2%) had four separate malignancies, including primary cancer of the colon, bilateral breast cancer, and lymphoproliferative disease.

Table 1. Female patients and disease characteristics.

Case	Age	Type	Site/type of initial primary cancer	Stage of initial primary cancer	Time interval	Site/type of second primary cancer	Stage of second primary cancer	Follow-up
1	66/F	Meta	NHL	IV	3 years	Endometrium	I	Progression of first primary, No reccurence for second
2	42/F	Meta	Breast	II	3 years	Coli uteri	II	Progression of both diseases
3	58/F	Meta	NHL	II	2 years	Caecum	I	Progression of first primary, No reccurence for second
4	52/F	Meta	Breast	II	3 years	Rectum	II	No reccurence for both
5	61/F	Meta	Breast	II	1 year	Colon	II	Progression
6	69/F	Meta	Endometrium	II	7 years	NHL	II	Stable disease
7	80/F	Meta	Breast	II	7 years	Sarcoma	II	Stable disease
8	64/F	Meta	Rectum	I	7 years	Kidney	I	No reccurence for both
9	58/F	Meta	Breast	III	7 years	Endometrium	I	No reccurence for both
10	74/F	Syn	Breast	III	3 months	Colon	II	No reccurence for both
11	62/F	Meta	Breast	II	7 years	NHL	III	No reccurence for both
12	77/F	Meta	Breast	I	9 years	NHL	IV	Progression of second primary
13	46/F	Syn	Breast	I	5 months	Coli uteri	II	No reccurence for both
14	83/F	Meta	Breast	II	5 years	Bladder	III	Progression of both diseases
15	58/F	Meta	Breast	II	15 years	NHL	II	No reccurence for both
16	56/F	Meta	Ovary	II	14 years	Lung	I	No reccurence for both
17	63/F	Meta	Breast	II	8 years	Lung	I	No reccurence for both
18	50/F	Syn	Melanoma mal	I	4 months	Breast	III	No reccurence for both
19	71/F	Meta	Breast	IV	5 years	Sigmoid	I	No reccurence for both
20	55/F	Meta	Breast	II	1 year	Breast	I	No reccurence for both
21	42/F	Meta	Ovary	IV	2 years	Breast	II	No reccurence for both
22	36/F	Meta	Breast	III	7 years	Ovary	II	No reccurence for both
23	67/F	Meta	Breast	II	2 years	Breast	I	No reccurence for both
24	75/F	Meta	Breast	II	6 years	Lung	IV	Stable disease
25	61/F	Syn	Breast	II	1 months	Lung	II	Progression of second primary
26	57/F	Meta	Breast	III	1 year	Rectum	I	No reccurence for both
27	55/F	Meta	Bladder	II	5 years	Lung	II	Progression of second primary
28	71/F	Meta	Breast	III	3 years	Colon asc.	I	No reccurence for both
29	46/F	Meta	Breast	II	6 years	Coli uteri	I	No reccurence for both
30	54/F	Meta	Ovary	I	6 years	Breast	II	Progression

Abbreviations: F-Female; Meta-metachronous cancer; Syn-synchronous cancer; NHL-non-Hodgkin lymphoma; MH-Morbus Hodgkin

In 45/50 (90%) patients, the lesions suggestive of the second primary tumor were with high metabolic activity. However, in five cases (5/50) second primary tumors showed limited F-FDG uptake with SUVmax being slightly above (two patients with indolent lymphoma) or less than 2.5 (patients with kidney, prostate cancer, and one sarcoma of the breast, respectively) (Figures 2, 3, and 4). If lesions presented any signs of malignancy on CT, even if they are hypometabolic on PET with SUVmax <2.5, they were also considered malignant.

In the female group, as a second malignancy we located eight UGC (8p, 26.6%), seven GIT cancers (7p, 23.3%), five breast cancers (5p, 10%), four lymphoma patients (4p, 12%), three pulmonary tumors (3p, 10%), two NET (2p, 6%), and one sarcoma (1p, 3%) with PET/CT. Most second primary cancers detected by PET/CT (81%; 17 of 21) were in the early stage (I or II).

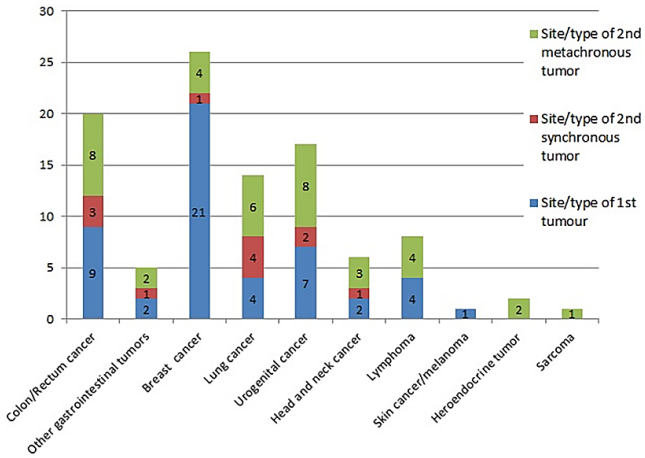

Figure 1. Site of initial primary cancer and side of detected synchronous and metachronous malignancies.

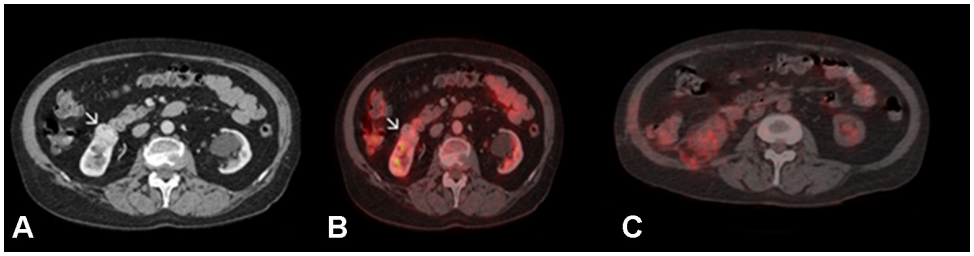

Figure 2. Positron emission tomography-computed tomography (PET-CT) in a 65-year-old woman with rectal cancer and a history of anterior rectal resection. Transaxial axial CT (A) and fused PET/CT (B) showed FDG non-avid lesion in the right kidney, highly suspicious for the second primary tumor. C) Transaxial fused PET-CT showing postoperative changes after biopsy confirmation of cancer and partial resection of the right kidney.

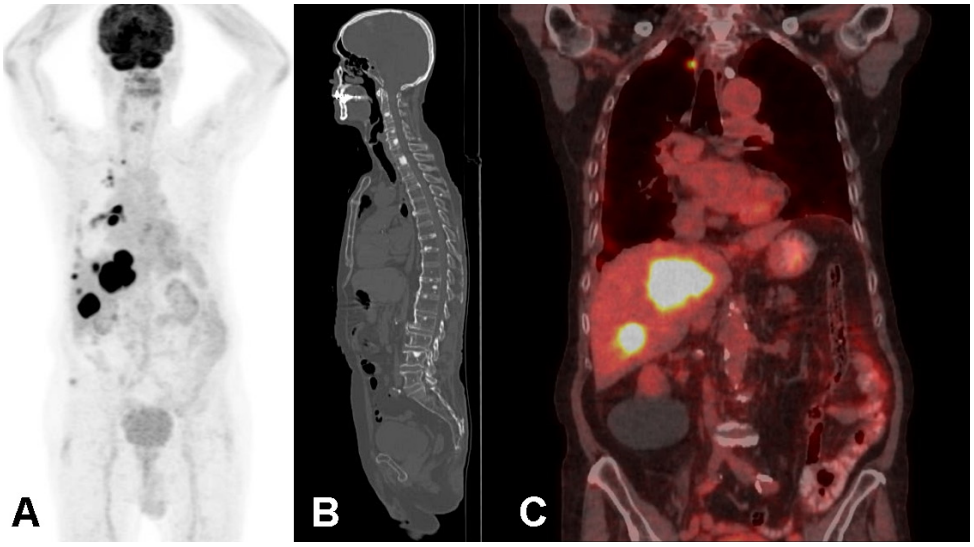

Figure 3. Positron emission tomography-computed tomography (PET-CT) in an 85-year-old man with rectal cancer and a history of anterior rectal resection. A, C) Coronal maximum-intensity-projection (MIP) and fused PET-CT images showing liver lesions with intensive FDG uptake (SUVmax 8.2) suggestive of the primary tumor metastatic disease and multiple FDG non-avid bone lesions. B) Sagittal CT images reveal sclerotic bone lesions highly suspicious for metastasis from prostate cancer. A prostate biopsy confirms the diagnosis.

In Table 1, we also noted 21 cases of breast cancer as a first tumor. Three of the cases were synchronous and the other eighteen were metachronous in their nature. In our study, there were six cases of second UGC (28.5%) and six with colon/rectum cancers (28.5%). In the other cases of the second primary malignancy, there were three NHL (14.3%), two breast carcinoma (9.5%), two lung cancers (9.5%), one bladder cancer (4.7%), and one carcinoid of the lung (4.7%), respectively. Among the other nine female patients (9/30) there were five tumors of the UGT, two NHL, one gastrointestinal cancer, and one malignant melanoma as a first primary tumor.

Concerning the therapy approach for the first primary cancers in the female group (Table 3), 97% (n=29) of patients had undergone surgery; 63% (n=19) received chemotherapy, 47% (n=14)-radiotherapy, and 33% (n=10) received another treatment (target- and/or hormonal therapy), demonstrating a high level of multimodality treatment regimen. Among second primary cancers, 77% of patients were undergone surgery; 50% (n=15) received chemotherapy, 17% (n=5) radiotherapy, and 10% (n=3) received another treatment (target- and/or hormonal therapy). We noticed a high level of surgery treatment (29 of 30 cases) and multimodality approach (24 of 30 cases) for the first cancer in the female group.

Overall, eighteen female patients had a complete response after therapy for both tumors and did not need further treatment (18p, 60%). Last imaging showed that nine patients had progression examined at least for one of the cancers (9p, 30%). Three patients with metachronous cancers had stable diseases although the therapy approach was changed accordingly (3p, 10%).

In our study, only two patients have confirmed genetic mutation (BRCA1 positive), sisters with first primary ovarian

and breast cancer at a young age. Due to the closer follow-ups, we detected a second primary tumor in the breast and ovary accordingly, both in the early stage. They were treated for their multiple primary tumors with curative intent and according to the last PET/CT exam, they were in a complete remission for their malignancies.

Analyzing the data in the male group, we noticed a group of 10 cases having a first primary tumor of the GIT (50%) (Table 2). When it comes to the second diagnosed tumors, we observed an equal split between gastrointestinal tumors and lung malignancies (each represented by 7, 35%) (Figure 5). Moreover, within those 14 second tumors, there was an exact split of synchronous and metachronous malignancies (3 and 4, respectively). Among these 20 male cancer patients, we have observed 14 patients in the third and fourth stages of their subsequent malignancy (70%).

Regarding the therapy approach for first primary cancers in the male group (Table 4), 85% (n=17) of patients had undergone surgery; 55% (n=11) received chemotherapy, 20% (n=4) radiotherapy, and 20% (n=4) received another treatment (target- and/or hormonal therapy). Concerning the therapy approach for second primary cancers, 55% of patients had undergone surgery; 65% (n=13) received chemotherapy, 20% (n=4) radiotherapy, and 15% (n=3) received another treatment (target- and/or hormonal therapy).

Evaluating the follow-up data, we found that sixteen patients had progression at the time of examination at least for one of the cancers (16p, 80%). Only two patients had complete responses after therapy for both tumors and did not need further treatment (2p, 10%). Two patients with synchronous cancers had stable diseases although the therapy approach was changed accordingly (2p, 10%).

As a result of the PET/CT study and the detection of a second primary tumor, the therapeutic plan of all 50 patients needs to be modified, although two patients refused further treatment and died within a few months. Analyzing the information in the metachronous group, we noticed that in 11 patients the first neoplasm is still active/advanced at the time of the diagnosis of second malignancy. The follow-up data showed that in 5 patients from this group the second neoplasm was at an early stage, which allowed a radical therapeutic approach. Evaluating the follow-up data, we found that in 10 patients (from 12) in the group of synchronous tumors, at least one of the malignant diseases was at an early stage.

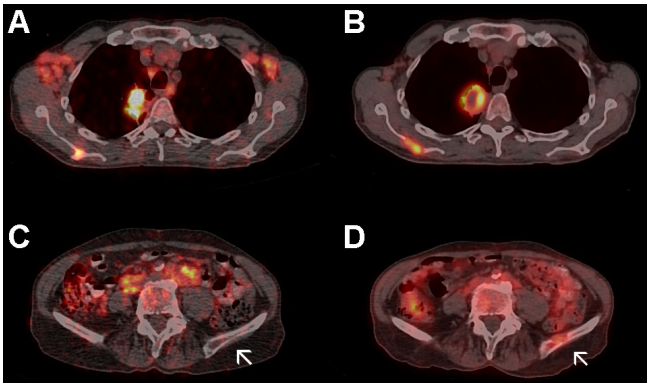

Figure 4. Positron emission tomography-computed tomography (PET/CT) in a 70-year-old man with a history of DLBCL 3 years ago. A, C) Transaxial fused PET-CT images show lymphadenopathy with limited F-FDG uptake (SUVmax 3.2) and (A) tumor formation in the right lung with intensive glucose metabolism (SUVmax 12.2) – highly suspicious for two different primary tumors. Biopsy confirmed the diagnosis of synchronous primary malignancies – indolent lymphoma and lung cancer. The restaging PET/CT (B, D) showed the complete metabolic response for indolent lymphoma, but the progression of the other malignant tumor-raising metabolic activity in the primary lung cancer and new bone lesions.

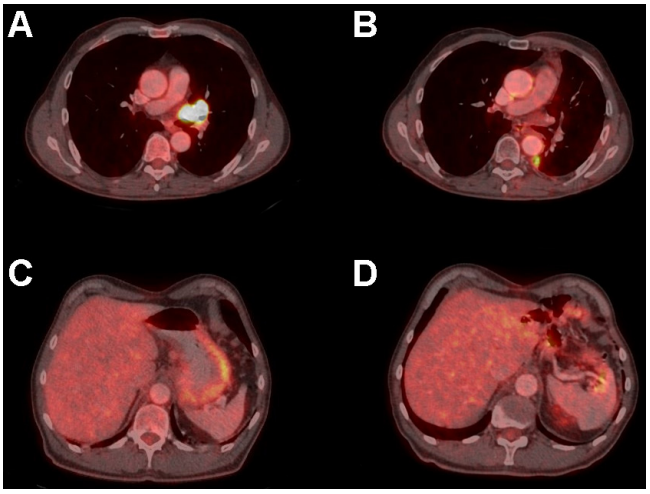

Figure 5. Positron emission tomography-computed tomography (PET/CT) in a 59-year-old man with histologically proven stomach cancer. C) Transaxial fused PET-CT preoperative images showed diffuse increased FDG uptake (SUVmax 5.2) in the stomach wall suggestive of the primary tumor. A) Transaxial fused PET-CT images revealed intensive FDG uptake (SUVmax 11.8) in tumor formation in the left lung, which is highly suspicious for lung cancer – biopsy confirmed the diagnosis. Same patient after therapy for both malignancies – gastrectomy and chemoradiotherapy. The restaging PET/CT (B and D) showed no evidence of recurrence and dissemination.

Discussion

Although the mechanisms responsible for the appearance of multiple primary cancers have not been fully explained, among the most frequent factors involved are treatment effects after chemo- and/or radiotherapy, exposure to carcinogens in the environment, the genetic susceptibility, the immune system of patients, and the interactions between them. Some genetic risk factors have been shown to predispose to multiple cancers [16]. If an individual has cancer at an unusually young age or has two or more primary cancers with distinct histological features, genetic testing should be considered, as these factors are indicative of an inherited cancer syndrome. A classic example is a hereditary breast and ovarian cancer syndrome, caused by mutations in genes like BRCA1 and BRCA2, and associated not only with breast

Table 2. Male patients and disease characteristics.

Case	Age	Type	Site of initial primary cancer	Stage of the initial primary cancer	Time interval	Site of the second primary cancer	Stage of the second primary cancer	Follow-up
1	84	Syn	Rectum	IV	3 months	Prostate	IV	Progression of both diseases
2	66	Meta	Prostate	II	2 years	Lung	II	Progression of second primary
3	56	Syn	Liver	II	4 months	Tongue	III	Progression of second primary
4	71	Meta	Rectum	III	7 years	Colon	III	Progression of both diseases
5	74	Syn	Lung	II	1 month	Colon	II	Stable disease
6	57	Syn	Stomach	II	1 month	Lung	II	No recurrence for both
7	68	Meta	Lung	II	15 years	Larynx	III	Progression of second primary
8	60	Meta	MH	IV	1 year	Larynx	IV	Progression of both diseases
9	70	Meta	Colon	III	3 years	Bladder	IV	Progression of both diseases
10	25	Meta	Colon	II	4 years	Stomach	IV	Progression of both diseases
11	70	Syn	NHL	III	1 month	Lung	IV	Progression of both diseases
12	70	Meta	Lung	II	2 years	Sigmoid	III	Progression of both diseases
13	79	Meta	Caecum	II	4 years	Duodenum	III	Progression of second primary
14	84	Meta	Prostate	II	5 years	Lung	IV	Progression of second primary
15	71	Meta	Colon	II	4 years	Lung	III	Progression of second primary
16	66	Syn	Lung	I	5 months	Rectum	I	No recurrence for both
17	64	Meta	Rectum	IV	2 years	Tonsil	IV	Progression of both diseases
18	78	Meta	Sigma	I	3 years	Lung	II	Progression of second primary
19	42	Syn	Oropharynx	III	2 years	Lung	I	Progression of second primary
20	68	Syn	Oropharynx	I	6 months	Oesophagus	III	Stable disease

Abbreviations: M-male; Meta-metachronous cancer; Syn-synchronous cancer; NHL-non-Hodgkin lymphoma

Table 3. Female patients, disease localization, and therapy approach.

First tumor type/localization	Breast 21	Lymphoma 2	Melanoma 1	Genital 2	GIT 1	Bladder 1
Treatment approach for the first tumor	Surgery 29	Radiotherapy 14	Chemotherapy 19	Hormone therapy 5	Target therapy 5	Multi-modality 24
Time elapsed between the tumors	Minimum 1 month	Maximum 15 years	Average 4.5 years			
Second tumor type/localization	Breast 5	Lung 3	GIT 7	Genital 6	Lymphoma 4	Bladder Kidney 2
	Sarcoma 1	NET 2				
Treatment approach for the second tumor	Surgery 24	Radiotherapy 5	Chemotherapy 15	Hormone therapy 1	Target therapy 3	Multi-modality 12

Abbreviations: GIT-gastrointestinal; NET-non-Hodgkin lymphoma

Table 4. Male patients, disease localization, and therapy approach.

First tumor localization	Lymphoma 2	Lung 4	H&N 2	GIT 10	Prostate 2	
Treatment approach for the first tumor	Surgery 17	Radiotherapy 4	Chemotherapy 11	Hormone therapy 1	Target Therapy 3	Multi-modality 10
Time elapsed between the tumors	Minimum 1 month	Maximum 15 years	Average 2.68 years			
Second tumor localization	Head and neck 4	Lung 7	GIT 7	Bladder 1	Prostate 1	
Treatment approach for the second tumor	Surgery 11	Radiotherapy 4	Chemotherapy 13	Hormone therapy 1	Target Immunotherapy 2	Multi-modality 9

Abbreviations: GIT-gastrointestinal; H&N-head and neck

and ovarian cancers but also with prostate, pancreatic cancer, and melanoma [17]. In our study, there were two cases of metachronous breast and ovarian carcinoma in two sisters with a confirmed BRCA1 mutation. The follow-up with PET/CT led to early detection of their second primary malignancies, allowed adjuvant therapy approach, and achievement of a complete therapeutic response. Some cancers tend to coincide due to the shared common environmental risk factors. Typical examples include smoking in lung cancer and cancers of the head and neck; dietary or endocrine factors in

various gynecologic cancers; ultraviolet light in melanoma and other skin cancers; viral agents in cervical and anogenital cancers [18–20].

Radiation field areas are high-risk locations for secondary tumors in patients who have undergone radiation therapy for a primary tumor. Chemotherapy-related secondary neoplasms usually develop at the site of contact (aero-digestive tract mucous membranes), site of absorption (gastrointestinal tract), or site of metabolism (liver) and excretion (kidneys, lungs) [21, 22]. The immunocompromised and overall poor physiological status of the patient would also play a role in the resistance [18]. The use of new therapeutic approaches like hormone and targeted therapies, immune modulation, and gene therapy, may also influence these mechanisms. Organ transplantations and continuous environmental carcinogen exposure may also be implicated as possible causal factors.

In patients with known cancer, work-ups often focus on the patient's primary disease, and incidental co-existence of another primary malignant lesion could be missed. Despite the relatively high cost, some reports also indicate that whole-body 18F-FDG PET has the potential of a screening method for detecting second malignancies and can significantly change patient management. Compared to conventional imaging modalities (US, CT, and MRI), the main advantage of F-FDG PET/CT is the whole-body protocol, which allows all tissues and organs to be evaluated in a single-step examination. Meanwhile, F-FDG PET/CT played an important role in staging, treatment selection, and follow-up of primary cancer [4–7].

Metastases of the known malignancy can also have an unusual type of dissemination, and separating an additional primary malignancy from an unusual metastatic disease can be challenging [23]. We used several clinical situations suspicious about the possibility of a second primary tumor in a patient with previously known malignancy based on the differential standard uptake value (SUV) of suspected lesions on PET-CT (e.g., lesions with very high SUV and lesions with low or normal SUV); atypical metastatic spread of primary tumor at staging or in follow-up (e.g., radiologically sclerotic bone metastases in rectum cancer); new metastatic spread or single metastatic lesion several years after a primary cancer diagnosis (e.g., enlarged cervical and supraclavicular lymph nodes); high tumor burden relative to tumor marker load (e.g., enlarged lymph nodes with low levels of tumor marker in breast cancer). Other clinical features should also alert clinicians to the possibility that a patient may have a second primary tumor, for example: in patients with exposure to epidemiological carcinogens (lifestyle or host factors); after prior chemotherapy (e.g., etoposide, anthracyclines) or after prior radiation therapy, especially if recurrence is in the prior irradiated field.

Of our patients, 64% had multimodality treatment therapy for their first cancer suggesting that this approach could play an important role in the development of MPM. Many of our FDG avid lesions were localized in the large intestine (22%), following the results from previous studies including patients with different primary tumors [24, 25]. Most of them (82%) were in the early stage (I or II), which provides a better opportunity for cure. Patients with lung cancer were 20% of the detected with PET/CT second cancers in our center, mostly in men, and all of them had poor prognoses independent from the first primary malignancy. Another 20% of the patients had second tumors of the urogenital system, mostly in the female group, all of them detected in the early stage with a good prognosis.

Worldwide, breast cancer (BC) is the most frequent cancer in women and the prognosis for BC is generally rather good, ranking the fifth cause of death from cancer overall. The most frequent first primary tumor in our group of patients was BC in women. We noticed that 86% of these patients had received radio- or chemotherapy alone, or underwent combined treatment for their first cancer (including target- or hormonal therapy) suggesting that this approach could play an important role in the development of MPM. Women with previous BC had an elevated risk of developing a second primary gynecologic cancer compared with the general population [20]. In our study, we observed a higher number of gynecological and gastrointestinal second primary tumors (59%). 81% of the patients in this group, detected by PET/CT were in the I or II stages, which provides a higher probability for cure.

However, we detected advanced stage second primary disease in 70% of the patients in the male group. This result could be explained either by the low compliance of patients to follow-up or by the tendency of neglecting symptoms in this group. This led to a predominance of the chemotherapy treatment in this group, in contrast to the therapeutic approach for the first tumor, where surgical treatment dominates.

There is no generalized and systematized published data in the literature, which demonstrates the role of 18F-FDG PET/CT in detecting synchronous and metachronous malignancies. We are still observing a lack of prospective studies in the scientific publication evaluating if the method can overcome the limitations and disadvantages of conventional imaging. Progress in this area will further consolidate the role of PET/CT as the reference standard in oncology. A few single-center retrospective studies evaluated the efficacy of PET scanning to screen asymptomatic individuals for cancer [11–12, 20, 26]. Mainly they showed a detection rate for synchronous and metachronous between 1.1% and 1.7%, most of them at the early curative stages [15, 27–29]. In addition, Ishimori et al. detected FDG avid lesions suggestive of additional primary tumors in 79 (4.1%) of 1,912 patients [30]. In our study, we assessed the efficacy of PET/CT in detecting unexpected additional FDG avid and non-avid malignant primary tumors in patients being evaluated for known malignancies, and we found that the prevalence of pathology-proven additional primary malignancy on PET/CT was 1.4%, which was comparable to the above-mentioned results.

The treatment of patients with multiple primary malignancies is challenging and should be discussed by a multi-

disciplinary team (MDT), especially in cases with synchronous primary tumors and metachronous malignancies when the first neoplasm is still active/advanced. In localized disease, treatment strategy may cover both malignancies, using radical surgery or radiation/chemoradiation. In the situation of advanced disease often, a therapeutic approach needs to be adapted and the prognosis is uncertain. However, analyzing the follow-up data of the patients in our group we noticed that 20% of them have such a therapeutic dilemma. Currently, the literature data on the management of patients with multiple primary malignancies is insufficient and it is important to collect information about as many cases as possible through cancer registries to identify an appropriate prevention strategy and potentially rare complications [23].

Our findings emphasize the added value of PET as a whole-body imaging technique, which provided important information above and beyond that for which the scan was ordered. The results of this study indicate the importance of follow-up and histological confirmation of these incidental findings, the majority of which were asymptomatic. Based on our PET/CT data, we were able to guide the biopsy, change the therapy approach, and follow up with all 50 patients for a long period.

A limitation of the present study was the lack of follow-up data for many patients, which were not included in the current study. Most of these patients were referred from an outside hospital for the PET/CT scan in our center and the contact with the referring physician and follow-up of the majority of the patients were somehow restricted. The results for these patients would probably increase the prevalence of additional malignancy but might also increase the false-positive rate. Other limitations include the retrospective nature of the study, a heterogeneous cohort of patients with multiple primary cancers, and previously received therapies in some of the patients before conducting PET/CT, which could influence the detection rate of second primary locations. In addition, the 18F-FDG PET/CT procedure is associated with significantly higher costs and a longer examination time.

Based on our observations, further research is necessary to make more accurate recommendations on the need for biopsy confirmation of FDG-avid lesions in patients with multiple primary cancer [29, 31]. In addition, FDG PET imaging may be used in the future as a screening test used in properly selected, high-risk groups.

In conclusion, as the focus in patients with multiple cancers is placed mainly on the primary disease, there is a higher likelihood of missing incidental co-existence of another primary malignancy. Therefore, every cancer patient, whether in complete clinical remission or not, should be regularly followed up through the entire lifespan.

PET/CT can identify a significant number of additional primary neoplasms in patients with known primary cancer, acquiring combined metabolic and morphologic information, as well as its whole-body protocol. This method can significantly modify the assessment of tumor dissemination and, therefore, change patient management substantially. Clearly, a comprehensive work-up of such identified lesions is essential, as a therapeutic strategy may be significantly dependent on such information. Newly PET/CT-identified subsequent primary lesions are often of early stage and thus have an excellent likelihood of being cured if treated promptly and aggressively.

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