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CASE REPORT

Differentiation of synchronous primary tumors through the discrepancy in intensity of [^{18}F]FDG uptake: Two case reports

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ABSTRACT

Synchronous primary tumors (SPTs) refer to the pathologically different tumors coexisting in an individual. This phenomenon is often identified during cancer evaluation using [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT). The two cases presented here highlight discrepancies in [^{18}F]FDG uptake intensity between the SPTs. Case 1 features a breast cancer with high uptake and a second primary lung cancer with low uptake, while Case 2 describes an esophageal cancer with low uptake and an incidental paraganglioma with high uptake. [^{18}F]FDG uptake varies by histopathological characteristics and is typically consistent within the same clonal group. A lesion showing discordant uptake relative to the primary tumor on [^{18}F]FDG PET/CT may indicate another distinct tumor.

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INTRODUCTION

Multiple primary neoplasms are not uncommon, occurring in 0.7% to 11.7% of all cancer patients [1]. Risk factors include viral infections, chemotherapy, radiation, gene mutations, smoking and environmental exposures [2]. Synchronous primary tumors (SPTs) specifically refer to two or more distinct tumors arising simultaneously or within six months in the same patient. Differentiating multiple primary tumors is crucial for treatment planning and prognosis, yet it remains challenging due to their unpredictable occurrence and metastasis. [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) is an effective tool in the oncology field for assessing disease extent and severity. Since [^{18}F]FDG uptake reflects molecular information and varies among tumor types, it can provide a clue for distinguishing SPTs. Here, two cases are presented focusing on metabolic discrepancies between double primary neoplasms. This case study was approved by the Institutional Review Board of Ilsan Paik Hospital on March 07, 2025 (IRB file No. ISPAIK 2025-02-027), and the need for informed consent was waived.

CASE PRESENTATION

Case 1

This case involved a 73-year-old woman with a palpable breast mass for 2 months. Ultrasonography revealed a 27 mm irregular hypoechoic mass with increased vascularity and hard elasticity in the right breast, along with a suspicious lymph node in the right axilla. Biopsy confirmed invasive ductal carcinoma with lymph node metastasis. A staging [^{18}F]FDG PET/CT scan showed a hypermetabolic primary tumor in the right upper outer breast with a maximum standardized uptake value (SUVmax) of 7.1, and a hypermetabolic metastatic lymph node in the right axillary level I (SUVmax=7.3) (Figure 1). Additionally, a 26 mm mildly hypermetabolic nodular lesion (SUVmax = 2.4) was detected in the right lower lobe of the lung, raising suspicion for malignancy and requiring differentiation between metastasis and primary lung cancer (Figure 1). Transbronchial biopsy of this lung lesion was initially attempted but failed to yield sufficient tissue; thus, surgical resection was planned. The patient underwent right partial mastectomy with axillary lymph node dissection and right lower lobectomy with mediastinal lymph node dissection on the same day. Adenocarcinoma (mucinous predominant) was confirmed in the lung. The final staging was T2N1aM0 for breast cancer and T1cN0M0 for lung cancer. Adjuvant chemotherapy, radiotherapy and hormonal therapy were administered for breast cancer. She is currently under regular surveillance with no recurrence of either cancer.

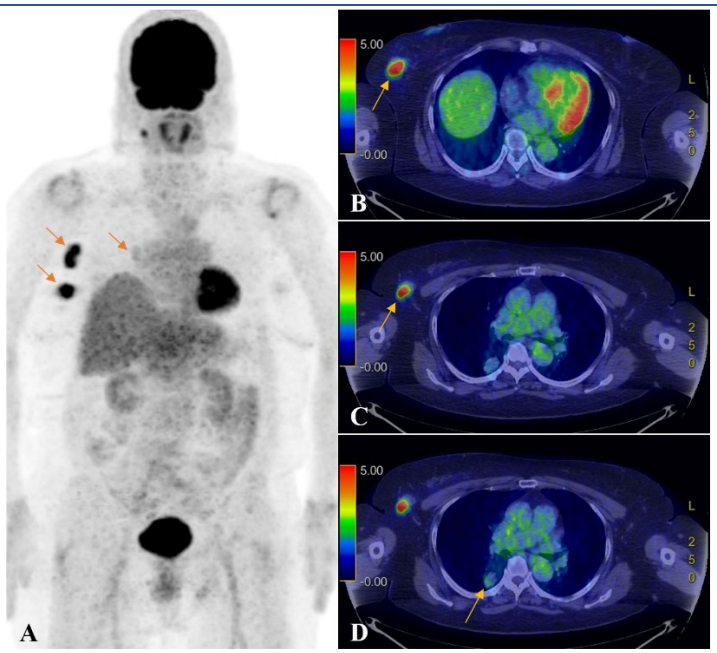

Figure 1. The MIP image (A) and axial fused images of the breast tumor (B), axillary metastatic lymph node (C), and lung tumor (D) on [^{18}F]FDG PET/CT. The breast cancer lesions showed high uptake of similar intensity, whereas the synchronous primary lung cancer exhibited low uptake

Case 2

This case involved a 77-year-old man diagnosed with esophageal cancer at a local clinic. Esophagogastroduodenoscopy at our institution revealed a 1.2 cm ulcerative lesion located 32cm from the upper incisor, and biopsy confirmed squamous cell carcinoma. Preoperative [^{18}F]FDG PET/CT demonstrated subtle uptake (SUVmax=2.1) in the primary tumor located in the mid-thoracic esophagus (Figure 2). A mildly hypermetabolic lymph node (SUVmax=3.8) with calcification was observed in the right paratracheal mediastinum, highly suggesting a reactive node (Figure 2). Additionally, an intense hypermetabolic well-defined nodular lesion measuring 22 mm (SUVmax=21.4) was identified in the abdominal aortocaval space (Figure 2), requiring differentiation between distant metastasis and another primary pathology. Ivor Lewis esophagectomy with mediastinal lymph node dissection and retroperitoneal mass removal were performed on the same day. The intra-abdominal tumor showed polygonal granular cellular proliferation, consistent with a sympathetic paraganglioma. The confirmed staging for esophageal cancer was T1bN0M0. He is currently under regular observation without recurrence of the two tumors.

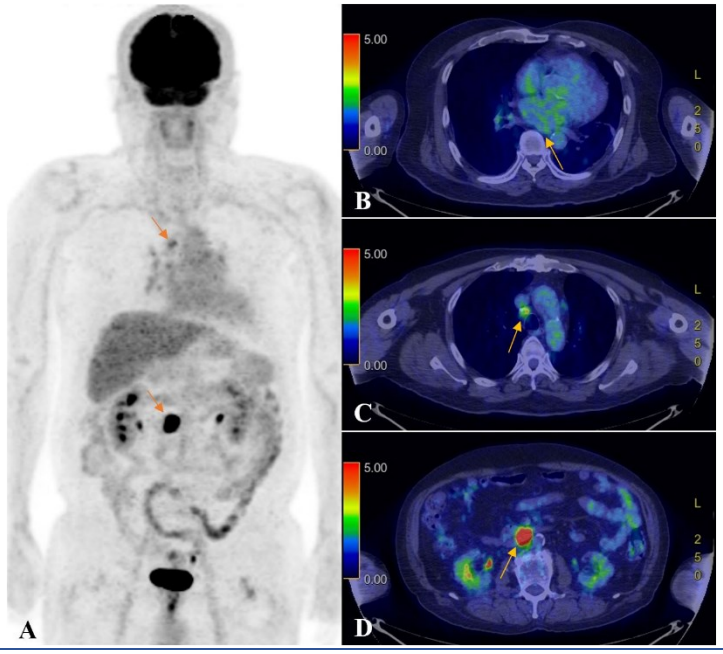

Figure 2. The MIP image (A) and axial fused images of the esophageal cancer (B), right paratracheal lymph node (C), and abdominal sympathetic paraganglioma (D) on [^{18}F]FDG PET/CT. The esophageal tumor showed low uptake which was barely noticeable on the MIP image, while the paraganglioma exhibited demonstrable uptake. The calcified mediastinal lymph node was confirmed to be reactive

DISCUSSION

In Case 1 presenting a breast cancer patient, double primary lung cancer was suspected because the solitary pulmonary nodule showed lower [^{18}F]FDG uptake than the other breast tumor lesions, despite its relatively large size. The degree of [^{18}F]FDG uptake is determined by several factors including overexpression of glucose transporters, upregulation of hexokinases and the cellular proliferation index [3]. Consequently, [^{18}F]FDG uptake varies by cancer type, histologic subtype and differentiation, reflecting each tumor's unique glucose consumption. Based on this physiology, some histologic cell types are known to exhibit high, low, or variable metabolic activity. For example, squamous cell carcinoma and aggressive lymphoma typically show high uptake. Breast lobular carcinoma and renal cell carcinoma usually show low uptake. Pulmonary adenocarcinoma demonstrates variable uptake, particularly showing lower uptake in the non-solid types. Thyroid cancer and hepatocellular carcinoma tend to exhibit higher [^{18}F]FDG uptake as their differentiation decreases. Our case followed these patterns, with high uptake in breast ductal carcinoma and low uptake in lung adenocarcinoma. This background knowledge

could be helpful in disease discrimination, though exceptions do occur.

Case 2 showed the opposite pattern of Case 1: low uptake in the primary esophageal cancer and high uptake in the suspicious lesion. Given the low endoscopic T-stage and the absence of regional lymph node metastasis, the intra-abdominal lesion with discordant uptake was unlikely to represent distant metastasis. [^{18}F]FDG uptake generally increases as tumor malignancy grade increases [4]. The low uptake observed in the early esophageal cancer in our case adhered to this principle. The intra-abdominal lesion was initially suspected to be a secondary high-grade malignancy due to its intense uptake. But atypically, it turned out to be a benign neurogenic tumor. Neurogenic tumors have variable uptake and even nonmetastatic tumors can exhibit high uptake [5]. In such cases, evaluating whether the lesion's shape and margin appear malignant may be helpful. Biopsy can also be considered.

The value of [^{18}F]FDG PET/CT in differentiating SPTs has been investigated in several studies. Luo et al. presented various cases highlighting discordant [^{18}F]FDG uptake between two different tumors, and suggested that combining PET/CT findings with specific serum tumor marker levels could enhance diagnostic accuracy [6]. Chen et al. found that [^{18}F]FDG PET/CT has higher sensitivity in detecting double primary cancers than conventional work-up [7]. Ilcheva et al. reported that [^{18}F]FDG PET/CT identified a significant number of additional primary tumors and could have a major impact on treatment strategy [8]. Gupta et al. underscored the advantage of whole-body coverage by PET/CT in detecting SPTs [9]. Karpinski et al. demonstrated a correlation in SUVmax values between primary lung tumors and their metastases, but a significant difference between primary and secondary lung tumors [10]. Both visual (qualitative) and SUVmax-based (semiquantitative) analyses can be utilized in identifying SPTs. Particularly, the maximum intensity projection (MIP) image provides a useful overview of uptake differences and distribution, facilitating the detection of SPTs.

On the other hand, there are some conflicting studies regarding the consistency of [^{18}F]FDG uptake between primary and metastatic lesions. Kosaka et al. reported that the SUVs of most metastatic lesions were within a similar range (from half to double) of the primary tumor's SUVs in lung cancer patients [11]. Similarly, Nguyen et al. found a positive correlation between SUV values of primary and metastatic lesions in lung cancer [12]. These are commonly accepted and easily understood concepts. However, other studies have described cases where metastatic lesions showed high uptake despite low uptake in the primary tumor, or vice versa [13, 14]. The factors contributing to such discrepancies remain unclear. For exceptional cases, evaluating whether the lesion's location and morphology align with typical metastatic patterns may prevent misdiagnosis.

In summary, the diagnostic algorithm for differentiating SPTs based on [^{18}F]FDG uptake is as follows: (1) Assess clinical information such as symptoms, medical history, family history and environmental risk factors. (2) Assess differences in [^{18}F]FDG uptake intensity across all lesions. Drawing on the aforementioned background knowledge, high-uptake pathologies (e.g., squamous cell carcinoma, high-grade lymphoma) typically present with SUVmax values of 8–10 or higher [15, 16], whereas low-uptake pathologies (e.g., breast lobular carcinoma, non-solid pulmonary adenocarcinoma) generally exhibit SUVmax values below 5 [17, 18]. (3) Assess differences in morphologic features such as shape, size, or necrosis among lesions on the underlying low-dose CT. (4) Assess lesion distribution patterns, with particular attention to whether they correspond to known metastatic pathways. (5) Perform histopathological confirmation for lesions with discordant characteristics. Multidisciplinary discussion may be helpful. In Steps 3–5, radiologic imaging can complement PET/CT by addressing its low spatial resolution and limited evaluability for non-[^{18}F]FDG-avid tumors. Conventional CT allows detailed visualization of lesion shape, margin and adjacent tissue invasion. Magnetic resonance imaging is effective for detecting low-uptake tumors (e.g., hepatocellular carcinoma, prostate cancer) and brain lesions obscured by surrounding physiologic [^{18}F]FDG uptake. Ultrasound is useful for superficial lesions (e.g., thyroid nodules, breast masses, lymph nodes) and is advantageous for guiding biopsies.

CONCLUSION

[^{18}F]FDG uptake reflects histopathological characteristics and biological aggressiveness. Therefore, discrepancies in uptake intensity may suggest the presence of pathologically different neoplasms. When lesions with discordant [^{18}F]FDG uptake are identified, nuclear medicine physicians should evaluate the possibility of SPTs and recommend additional imaging modalities or biopsy to clinicians to assist in differential diagnosis. Long-term monitoring should also be

recommended due to the potential for asynchronous progression and increased risk for subsequent malignancies.

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