Utility of different positron emission tomography/computed tomography tracers in the evaluation of incidentally detected dual malignancies: An experience from a tertiary care center

ABSTRACT
Multiple primary malignancies in a cancer patient are not a rare occurrence. The most common presentation of multiple primary malignancies is dual malignancies. The usefulness of different positron emission tomography (PET)/computed tomography (CT) tracers in the evaluation of dual synchronous primary malignancies is not well documented. Here, we present a case series, where two patients, referred for PET/CT, after being diagnosed with one primary malignancy were found to be having a second primary malignancy, diagnosed incidentally in PET/CT, further validated by PET/CT with another tracer.

Keywords: Dual malignancies, fluorodeoxyglucose positron emission tomography/computed tomography, positron emission tomography/computed tomography tracers, prostate-specific membrane antigen positron emission tomography/computed tomography

INTRODUCTION
Multiple synchronous or metachronous malignancies in a single cancer patient are not a rare occurrence. Although $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is the workhorse of positron emission tomography (PET) imaging, the main disadvantage of $^{18}$F-FDG is its limited utility in few malignancies such as prostate cancer, hepatocellular carcinoma (HCC), neuroendocrine tumors (NETs), and renal cell carcinoma, due to varying tumor biology mechanisms. In this case series, we have demonstrated the utility of other PET tracers such as $^{68}$Ga-labeled prostate-specific membrane antigen (PSMA) in complementing the role of $^{18}$F-labeled FDG in diagnosis of dual malignancies in patients.

CASE REPORTS

Case no. 1
A 73-year-old patient, a recently diagnosed case of carcinoma prostate, was referred for $^{68}$Ga PSMA PET/computed tomography (CT) scan for staging. MIP $^{68}$Ga PSMA PET/CT scan [Figure 1b] revealed $^{68}$Ga PSMA avid lesions in the prostate gland, corresponding to the known carcinoma prostate [white arrow in Figure 1B1] with multiple non-PSMA avid lesions in the liver, multiple osteolytic skeletal lesions with multiple non-PSMA avid cervical, mediastinal, and abdominal lymph nodes [Figure 1B3-1B4], and suspicious of tuberculosis or synchronous malignancy. In view of suspicion...
of synchronous malignancy or tuberculosis, the patient underwent an 18F-FDG PET/CT scan. The MIP 18F-FDG PET/CT scan [Figure 1a] showed 18F-FDG uptake in discrete and coalescent lesions in the liver, multiple osteolytic skeletal lesions, and multiple cervical, mediastinal, and abdominal lymph nodes [Figures 1A1-1A4]. The 18F-FDG PET/CT scan showed no significant 18F-FDG uptake in the lesions in the prostate gland. Thus, the 18F-FDG PET/CT increased the chances of dual pathologies in the patient. Histopathology from the mediastinal lymph nodes demonstrated features of mantle cell lymphoma, confirming the diagnosis of synchronous malignancy in the patient.

Case no. 2
A 73-year-old patient, a recently diagnosed case of carcinoma prostate, was referred for 68Ga PSMA PET/CT scan for staging. 68Ga PSMA PET/CT scan [Figure 2b] revealed prostatomegaly with multiple 68Ga PSMA avid lesions in the prostate with extension to urinary bladder and bilateral seminal vesicles with multiple PSMA avid iliac lymph nodes [Figure 2B1 and B2], with non-PSMA avid mediastinal and parasternal lymph nodes with mass formation [Figure 2B3 and B4], and suspicious of tuberculosis or synchronous malignancy. In view of suspicion of synchronous malignancy or tuberculosis, the patient underwent an 18F-FDG PET/CT scan. The 18F-FDG PET/CT scan [Figure 2a] showed intensely 18F-FDG avid mediastinal and parasternal lymph nodes with mass formation [Figure 2A3 and A4]. The 18F-FDG PET/CT scan showed mild 18F-FDG uptake in the lesions in the prostate gland [Figure 2A1] and iliac lymph nodes [Figure 2A2]. Thus, the 18F-FDG PET/CT increased the chances of dual pathologies in the patient. Histopathology from the mediastinal lymph nodal mass formation demonstrated features of diffuse large B cell lymphoma, confirming the diagnosis of synchronous malignancy in the patient.

DISCUSSION
Multiple primary malignancies in a cancer patient are not a rare occurrence. The diagnosis of a second or a third primary is not easy to arrive at due to the possibility of recurrent or secondary lesions from the known existing primary malignancy.[11] Timely diagnosis and appropriate management can alter the overall prognosis and survival in multiple primary malignancies. The first case of multiple primary malignancies was described by Billroth in 1889.[12] The most common presentation of multiple primary malignancies is dual malignancies.[11] Multiple primary malignancies can be divided into synchronous or metachronous on the basis of the time interval between the diagnosis of the two
primaries. Synchronous or “simultaneous” malignancies are those primary tumors that occur in the same patient within 6 months of each other, whereas metachronous or “interval” malignancies are those that occur in the same patient separated by a period of more than 6 months. PET/CT is a technological advancement having a significant impact in oncology. Currently, $^{18}$F-FDG represents the workhorse in oncological PET/CT imaging. The basis for using FDG in oncology was demonstrated by Warburg, who observed an increase in glycolytic activity in cancer cells under both aerobic and anaerobic conditions. The main disadvantage of $^{18}$F-FDG is that it is not a specific oncological tracer, as several malignancies (i.e., prostate cancer, HCC, NETs, renal cell carcinoma) cannot be adequately assessed by $^{18}$F-FDG PET. Therefore, other new radiopharmaceuticals have been developed that are capable of giving more specific information, leading to better sensitivity and specificity or just complementing $^{18}$F-FDG PET results.

The most important characteristic of NETs is the expression of somatostatin receptors (SSTR) on their cell membrane, namely SSTR1–5. The SSTR2, SSTR3, and SSTR5 subtypes are particularly overexpressed on the cell membranes of NETs in most of the cases. Various $^{68}$Ga-DOTA-peptides show affinity to SSTR2, SSTR3, and SSTR5 and are excellent candidates for imaging and staging patients with NETs, including the localization of primary tumors in patients with known NET metastasis (carcinoma of unknown primary origin with sensitivity and specificity ranging from 97% to 100% and 96% to 100% in various series). Since NETs are heterogeneous group of neoplasm and tumor heterogeneity cannot be completely assessed by tumor biopsy because limited tissue in some cases may not give accurate Ki-67 index value. The Ki-67 index value may vary in primary and metastatic lesions, or it may vary over time in the same patient in response to treatment and progression of the disease. Thus, dual-tracer imaging with $^{68}$Ga-DOTANOC and FDG PET/CT scan may reflect different aspects of tumor biology, SSTR expression, and glucose metabolism. However, dual-tracer imaging is helpful in patients with Ki-67 index >10%.

PSMA is a cell surface protein expressed abundantly in prostate carcinoma cells. While choline metabolism has not increased in a large number of cases, PSMA is overexpressed in most prostate carcinoma. $^{68}$Ga-labeled PSMA ligands can detect prostate cancer relapses and metastases with high sensitivity. Liver metastases are the third most common site for systemic spread in prostate cancer after bone and lung. $^{68}$Ga PSMA PET/CT scan can produce false-negative liver metastases in advanced metastatic castration-resistant prostate cancer as they lose PSMA expression. A possible explanation for the same could be the diversity of phenotypes in metastases. In prostate cancer, liver metastases are frequently associated with neuroendocrine differentiation characteristics. In our cases, the non-PSMA avid liver lesions were initially suspected to be prostate cancer metastases; however, since there were many other non-PSMA avid lesions, FDG PET/CT scan was advised and this scan demonstrated multiple FDG avid and later biopsy confirmed diagnosis of lymphoma also. The usefulness of dual-tracer PET/CT in evaluating dual synchronous primary malignancies is not well documented.

Our two cases were carcinoma prostate and lymphoma; thus, $^{18}$F-FDG and PSMA PET tracers helped in reaching the diagnosis. In these patients, the second PET/CT was advised to look for the most appropriate site of biopsy to characterize nontracer avid lesions in the first PET/CT scan and in case of second malignancy to stage the other malignancy. After review of literature, we came across only one case report describing role of dual PET/CT tracer in the evaluation of dual malignancies. Rest of the case reports described role of dual PET/CT tracer imaging in the evaluation of single malignancy. Here, we report an interesting case series about the use of dual-tracer PET/CT in the evaluation of in dual primary malignancies.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bagri PK, Singh D, Singhal MK, Singh G, Mathur G, Jakhar SL, et al. Double primary malignancies: A clinical & pathological analysis report from a regional cancer institute in India. Iran J Cancer Prev 2014;7:66-72.
2. Billroth T. General Surgical Pathology and Therapy in 51 Lectures: A Handbook for Students and Physicians. 14th ed. Berlin, Germany: G. Reimer; 1889. p. 908.
3. Lee JS, Moon W, Park SJ, Park MI, Kim KJ, Jang LL, et al. Triple synchronous primary cancers of rectum, thyroid, and uterine cervix detected during the workup for hematochezia. Intern Med 2010;49:1745-7.
4. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. Cancer 1961;14:221-30.
5. Miele E, Spinelli GP, Tomao F, Zullo A, De Marinis F, Pasciuti G, et al. Positron emission tomography (PET) radiotracers in oncology – Utility of $^{18}$F-fluo-deoxy-glucose (FDG)-PET in the management of patients with non-small-cell lung cancer (NSCLC). J Exp Clin Cancer Res 2008;27:52.
6. Lopci E, Nanni C, Castellucci P, Montini GC, Allegri V, Rubello D, et al. Imaging with non-FDG PET tracers: Outlook for current clinical applications. Insights Imaging 2010;1:373-85.
7. Bombardieri E, Maccauro M, De Deckere E, Savelli G, Chiti A.
Nuclear medicine imaging of neuroendocrine tumours. Ann Oncol 2001;12 Suppl 2:S51-61.
8. Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. Eur J Nucl Med Mol Imaging 2010;37:67-77.
9. Ambrosini V, Nanni C, Zompatori M, Campana D, Tomassetti P, Castellucci P, et al. (68)Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2010;37:722-7.
10. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology 1998;52:637-40.
11. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga] gallium-labelled PSMA ligand for the diagnosis of prostate cancer: Biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging 2013;40:486-95.
12. Barrett JA, Coleman RE, Goldsmith SJ, Vallabhajosula S, Petry NA, Cho S, et al. First-in-man evaluation of 2 high-affinity PSMA-avid small molecules for imaging prostate cancer. J Nucl Med 2013;54:380-7.
13. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, et al. Biodistribution, tumor detection, and radiation dosimetry of (18)F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med 2012;53:1883-91.
14. Ho CL, Chen S, Leung YL, Cheng KC, Wong YH. Dual-tracer PET/CT differentiates 2 types of primary cancers and metastases in a patient with crossed fused renal Ectopia. Clin Nucl Med 2019;44:157-8.
15. Vardhanabhuti V, Lo AW, Lee EY, Law SY. Dual-tracer PET/CT using (18)F-FDG and 11C-acetate in gastric adenocarcinoma with liver metastasis. Clin Nucl Med 2016;41:864-5.
16. Gupta N, Dougall P, Mahawar S. Primary ovarian carcinoid and DOTANOC positron emission tomography-computed tomography scan. World J Nucl Med 2019;18:69-70.