18F- FDG-PET/CT for the Diagnosis of Tumor Thrombosis

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ABSTRACT: **Background:** Venous thromboembolism is a well-recognized and relatively frequent complication of malignancy, whereas tumor thrombosis is a rare complication of solid cancers. The correct diagnosis of tumor thrombosis and its differentiation from VTE can alter patient management and prevent unnecessary long-term anticoagulation treatment.

Objectives: To evaluate the contribution of 18F-fluorodeoxyglucose positron emission tomography/computed tomography to the diagnosis of tumor thrombosis and its differentiation from VTE.

Methods: PET/CT scans from 11 patients with suspected tumor thrombosis were retrospectively evaluated. Suspicion arose from positive PET/CT in eight cases, or from findings on contrast-enhanced CT in three patients. Criteria for positivity of PET/CT included increased focal or linear uptake of 18F-FDG in the involved vessel. Findings were categorized as PET/CT positive, or PET/CT negative and compared to contrast-enhanced or ultrasound Doppler, pathology where available, and clinical follow-up.

Results: Eight occult tumor thromboses were identified by PET/CT-positive scans. Underlying pathologies included pancreatic, colorectal, renal cell, and head-neck squamous cell carcinoma, as well as lymphoma (4 patients). Three thrombotic lesions on contrast-enhanced CT were PET/CT negative, due to VTE (2 patients) and leiomyomatosis. Accuracy of PET/CT to differentiate between tumor thrombosis and benign VTE was 100% in this small study.

Conclusions: Contrast-enhanced CT defines the extent of thrombotic lesions, while the functional information from PET/CT characterizes the lesions. It appears that PET/CT may be helpful in the diagnosis of occult tumor thrombosis and its differentiation from VTE. *IMAJ* 2009;11:69–73

KEY WORDS: tumor thrombosis, venous thromboembolism, PET/CT, contrast-enhanced CT

Venous thromboembolism is a well-recognized and relatively frequent complication of malignancy. Tumor thrombosis, in contrast, is a rare complication of solid cancers such as colon, pancreas, hepatocellular and renal cell carcinomas, and has also been described in lymphoma and sarcoma [1]. The correct diagnosis of tumor thrombosis and its differentiation from VTE can alter patient management and prevent unnecessary long-term anticoagulation treatment.

Only sporadic reports have described the diagnosis of tumor thrombosis by positron emission tomography with 18F-fluorodeoxyglucose [2-11]. Perhaps owing to the rarity of the condition, the largest series in the literature to date described six cases of tumor thrombosis diagnosed by PET performed with simultaneous computed tomography [1]. Although only limited data exist in the literature, it appears that 18F-FDG-PET scans can be used to accurately differentiate between septic and aseptic deep vein thrombosis [12,13]. Septic lesions have increased uptake of 18-FDG, whereas aseptic deep vein thromboses have been reported to exhibit normal biodistribution of the agent. These findings were the basis for the assumption that FDG imaging by PET/CT may differentiate between tumor thrombosis and VTE as well. The present study is a retrospective evaluation of the contribution of PET/CT to the diagnosis of tumor thrombosis, and the differentiation between tumor thrombosis and thromboembolic phenomena.

PATIENTS AND METHODS

The PET/CT scans of 11 patients with suspected tumor thrombosis (7 males, 4 females, age 31–76 years) were retrospectively evaluated. Nine patients had oncologic or hemato-oncologic disease. Suspicion arose from positive PET in eight cases and from findings on contrast-enhanced CT in two patients. Patient 9, with a history of non-Hodgkin's lymphoma, had undergone contrast-enhanced CT due to abdominal pain and suspected recurrence of the lymphoma. The contrast-enhanced CT, performed prior to the PET/CT, was interpreted as normal at the time, and the patient was referred for further evaluation by PET/CT. Revision of the contrast-enhanced CT at the time of PET/CT interpretation disclosed thrombosis of the uperior mesenteric vein. Overall, five patients were referred for evaluation of lymphoma (three non-Hodgkin's, two Hodgkin's disease), one had recurrence of colorectal carcinoma, one had renal cell

VTE = venous thromboembolism
PET/CT = positron emission tomography/computed tomography
FDG = fluorodeoxyglucose

carcinoma, one had recurrence of pancreatic carcinoma, and one had recurrent squamous cell carcinoma of the head and neck. Two patients (#10 and 11) were referred for further evaluation and characterization of lesions in and around the heart – one with a heterogenous hyperdense mass seen in the right ventricle, the other with a non-specific mass lesion, possibly thrombosis, in the inferior vena cava extending into the right atrium. Neither patient had cancer or known risk factors for VTE, and before considering invasive diagnostic procedures both were referred for further evaluation of the lesions by PET/CT.

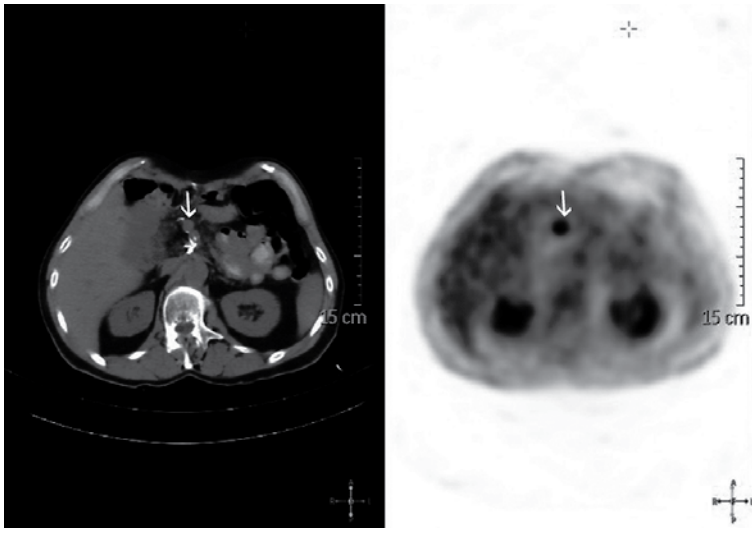
IMAGING METHOD

All patients were imaged with a Gemini PET/CT Imaging System (Philips, USA) which provided three-dimensional acquisition, processing and display of CT, PET and PET/CT images, with 6.0 mm PET spatial resolution and a dual slice Mx800 EXP CT scanner. Whole-body PET/CT imaging was performed in fasting patients (4–6 hours) after intravenous administration of 370 MBq (10 mCi) of 18F-FDG. Oral, but not intravenous contrast was administered. After a 60 minute uptake period, during which patients were instructed to rest quietly, the images were acquired. First, a CT surview (30 mA, 120 kVp, field of view 500 mm, length of scan 1.0–1.5 m with a speed of 100 mm/sec and a spatial resolution of 1 mm) was performed from the tip of the skull to the level of the proximal thigh. This was followed by a dual slice CT (50 mAs per slice, 120 kVp, with a slice thickness of 5 mm, length of scan according to the result of surview, with a bed speed of 20 mm/sec, rotation time 0.75 sec, and a pitch of 1.5, and FOV 600 mm). Finally, the acquisition of PET emission images was performed (2–3 minutes per bed position of 8.4 cm). The total acquisition time, accumulating between 100 and 150 million useful events, varied between 25 and 35 minutes per patient. The CT data were used for attenuation correction of PET emission images, and for fusion with PET data for accurate localization of lesions. Non-attenuated data were reconstructed after scan acquisition had been completed. Reconstruction of attenuation corrected data was executed concurrently. All digital images were interpreted on a dedicated Syntegra workstation.

INTERPRETATION OF RESULTS

PET/CT findings were categorized as either PET positive or PET negative. Criteria for positive PET included increased focal or linear uptake of 18F-FDG in the involved vessel, with standard uptake value above 2.5, and positive findings were localized to anatomic images from the non-enhanced CT. PET/CT findings were compared with concurrent contrast-enhanced CT (10 cases), in one case (patient 5) with ultrasound Doppler, and in one case also with histopathology (patient 11). With the exception of one patient who died (patient 5), all patients underwent repeated imaging to evaluate response to anticoagulation (2 patients) or to chemotherapy (7 patients). The patient with pathologically proven leiomyomatosis (patient 11) was not re-imaged. Results were verified by clinical follow-up and comparison with post-treatment imaging results. Follow-up imaging proved resolution of all thrombotic lesions and concluded that the appropriate treatments – chemotherapy or anticoagulation – had been administered.

Figure 1. PET/CT: Transaxial slices of PET/CT in a patient with pancreatic carcinoma 1 year after Whipple operation. PET (right, arrow) depicts a focus of increased uptake of 18F-FDG corresponding on non-contrast-enhanced CT to the anatomic location of superior mesenteric vein (left, arrow). The findings are consistent with a hypermetabolic lesion in the vessel region, suggestive of tumor thrombosis.

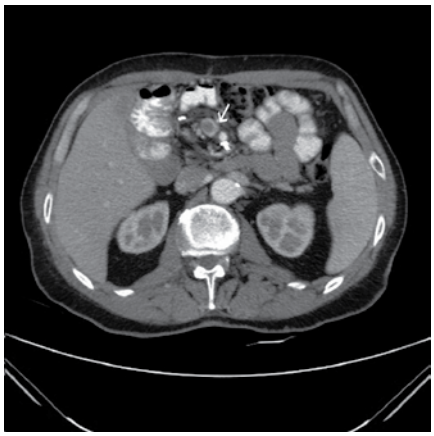


RESULTS

Of the 11 scans reviewed there were 8 cases of tumor thrombosis identified initially by PET/CT, with 6 being interpreted as foci of increased uptake of 18F-FDG [Figures 1 and 2], and 2 as increased linear uptake along the vessel (patients 5 and 8) [Figure 3]. Seven of eight patients with positive PET findings had intraluminal vascular defects on corresponding contrast-enhanced CT, consistent with thrombosis. In one patient (patient 5) the diagnosis of tumor thrombosis was confirmed before treatment with ultrasound Doppler. All three patients referred with known contrast-enhanced CT findings had negative PET/CT and tumor was effectively ruled out. These PET/CT negative findings were proven by clinical and imaging follow-up to be due to benign VTE in two patients (patients 9 and 10), and one case of intravenous leiomyomatosis (patient 11) was confirmed by histopathol-

FOV = field of view

Figure 2. Transaxial slice of contrast-enhanced CT in the same patient (pancreatic cancer) depicts marginal enhancement and intraluminal filling defect in the superior mesenteric vein (arrow), consistent with non-specific intravascular thrombus



ogy. Bone marrow biopsy determined polycythemia vera as the underlying pathology in patient 10. PET/CT correctly differentiated between tumor thrombosis and benign venous thrombosis, detecting tumor thrombosis with 100% accuracy in this small group.

Overall, the CT component of PET/CT, performed without intravenous contrast, could, at best, suggest the presence of vascular pathology. On the other hand, contrast-enhanced CT, while easily demonstrating intraluminal vascular filling defects, could not differentiate between tumor thrombosis and VTE. The information from the contrast-enhanced CT, however, provided information regarding the exact extent of the thrombotic lesions.

All demographic and clinical data, including indications for referral to PET/CT and scan results, are summarized and presented in Table 1. The 11 patients described here were derived from a large population of oncology patients referred to the PET/CT service but the prevalence of the phenomenon in the population was not evaluated.

DISCUSSION

Tumor thrombosis is a relatively rare complication of solid cancers, with occult inferior vena cava tumor thrombosis having a reported incidence rate of 0.11% [1]. Sporadic reports have described the diagnosis of tumor thrombosis by PET/CT in various types of cancer including pancreatic [2], colon [5,6], renal cell [3], adrenocortical [2], thyroid [10] and osteosarcoma [9]. The largest series published to date described six cases, all stemming from the above-mentioned etiologies (renal cell carcinoma, adrenal, pancreas), as well as Ewing sarcoma, lymphoma and hepatocellular carcinoma [1].

Interestingly, four of eight patients with tumor thrombo-

Figure 3. Representative coronal slices of PET/CT in a patient with suspected recurrence of colorectal carcinoma. Increased linear uptake is seen corresponding to the anatomic location of the superior mesenteric vein and its branches. The additional hypermetabolic finding in the lower right quadrant was consistent with recurrent tumor in the region of the cecum.

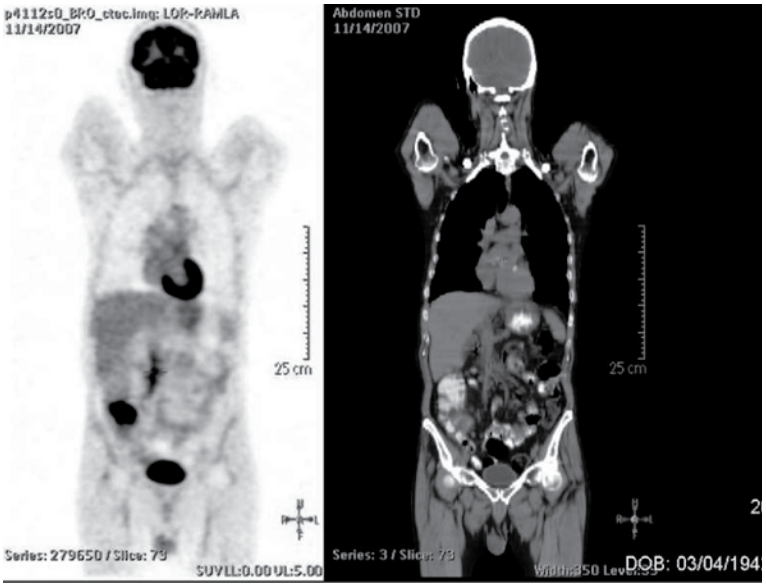


Table 1. Summary of demographic and clinical data, and imaging results

Patient #	Gender/ Age	Underlying disease	Indication for scan	Involved vessel	PET/CT (+,-)	Outcome treatment	Follow-up
1	M/42	NHL	Staging	Iliac vein	+	TP, chemo	Repeat PET/CT
2	F/31	Mediastinal NHL	Staging	SVC	+	TP, chemo	Repeat PET/CT
3	M/64	Pancreatic cancer	Suspected recurrence	SMV	+	TP, chemo	Repeat PET/CT
4	F/33	HD	Staging	SVC	+	TP, chemo	Repeat PET/CT
5	M/57	Renal cell cancer	Restaging	IVC	+	TP , chemo	Died
6	M/72	Squamous cell cancer	Restaging	Jugular vein	+	TP, chemo	Repeat PET/CT
7	F/31	HD	Staging	Subclavian vein	+	TP, chemo	Repeat PET/CT
8	M/66	Colon cancer	Suspected recurrence	SMV	+	TP, chemo	Repeat PET/CT
9	M/62	NHL	Suspected recurrence, reevaluation of CT	SMV	-	TN, AC	2
10	M/76	Unknown primary	Evaluation of CT finding	Right ventricle	-	TN, AC (PV)	Repeat contrast-enhanced CT
11	F/49	Unknown primary	Evaluation of CT finding	IVC and right atrium	-	TN, AC (leiomyomatosis)	—

NHL = non Hodgkin's lymphoma, HD = Hodgkin's disease, IVC = inferior vena cava, SVC = superior vena cava, SMV = superior mesenteric vein, TP = true positive, TN = true negative, chemo = chemotherapy, AC = anticoagulant, PV = polycythemia vera.

sis in our group had lymphoma (two Hodgkin's disease, two non-Hodgkin's lymphoma). Though this seems a dominant component of this small group, it may merely reflect the fact that lymphoma patients comprise more than 50% of referrals to our service. However rare, the entity should be recognized by those involved in the management of lymphoma patients, since both tumor thrombosis and VTE are possible complications of the disease [14,15]. Patient 9 exemplifies this statement: the contrast-enhanced CT lesion (intravascular filling defect), without corresponding FDG uptake, allowed the diagnosis of mesenteric vein VTE, which was consequently treated appropriately by anticoagulants.

The remaining four patients in the group with diagnosis of tumor thrombosis had pancreatic, colorectal, renal cell and squamous cell carcinoma of the head and neck. The latter case is interesting because tumor thrombosis from such an etiology has not been diagnosed previously by PET. However, there is a report of a positive PET finding in an "aseptic thrombus" seen in a patient with squamous cell carcinoma of the tongue [12]. In view of the use of 18F-FDG-PET scans to accurately differentiate between septic and aseptic deep vein thrombosis [13], the increased uptake observed in the aseptic thrombus in the squamous cell carcinoma-tongue patient raises the question as to whether that patient perhaps had tumor thrombosis as well. If so, physicians treating patients with head and neck tumors should be aware of the rare but possible complication of tumor thrombosis and the benefit that may be obtained by utilizing PET/CT for its diagnosis.

PET/CT allows whole-body imaging and the efficient identification of pathology both above and below the diaphragm. While most previously reported PET-positive tumor thombi involved abdominal cancers and primarily lesions in the inferior vena cava, five patients in our study had lesions above the diaphragm. The tumor thombi seen in jugular and subclavian veins, and those in the superior vena cava, are noteworthy, because despite being rare [16] these supra-diaphragmatic findings comprised 50% (4/8) of the tumor thrombosis cases observed in this group. Physiological uptake of 18F-FDG in the heart most commonly affects visualization of the left ventricle, and thus need not interfere with interpretations of right-sided cardiac chamber lesions such as those described here. The infradiaphragmatic findings (three superior mesenteric vein lesions, two being tumor thrombi found in pancreatic cancer and colorectal cancer patients, and the third VTE demonstrated in a lymphoma patient) also highlight the need for a tool to differentiate between the two entities, and the ability of PET/CT to serve as that tool.

While other imaging data have been fused, and, in fact, cardiac tumor has been differentiated from thrombus by combined magnetic resonance imaging and F18-FDG-PET imaging [4], PET/CT is the most readily available multimodality imaging technique to date, and its use is therefore recommended in clinical settings such as those reported here.

While the study group described here was small, and results indicated both 100% sensitivity and specificity for diagnosis of occult tumor thrombosis, mention must be made of potential pitfalls. False positive PET findings may be due to inflammatory lesions, including infected catheters in the venous vasculature which have been demonstrated with increased uptake of FDG [17,18]. All positive PET findings correlated to other imaging and clinical data, and there were no false positive results in this group. In contrast, missed diagnoses may relate to the size of the lesion, or the avidity of the underlying pathological process to FDG. Intravascular pathology cannot be identified by CT without the aid of contrast enhancement, such that, in effect, tumor thrombosis arising from non-FDG avid primary tumors could be missed entirely by our methodology. However, since most practicing physicians are aware of the dependency on FDG avidity, such occurrences are expected to be rare.

Of the 11 patients in our group, 8 had positive PET findings that were consequently confirmed as intravascular lesions by contrast-enhanced CT (in 7 cases) or, in one case (inferior vena cava of renal cell carcinoma, patient 5) by ultrasound Doppler. Three other patients, with ultimately negative PET/CT, came to the PET/CT service with intravascular lesions on contrast-enhanced CT (2 were known and 1 was "missed" and diagnosed retrospectively). All three contrast-enhanced CT lesions, which were further evaluated for possible FDG uptake, were larger than the 0.6 cm limit of resolution of the PET. Of these three, polycythemia vera was diagnosed as the cause for VTE in one case, and VTE of the superior mesenteric vein was diagnosed clinically in another. In the third case, benign leiomyomatosis was eventually proven by postoperative histopathology. Leiomyosarcoma may have theoretically been a "missed" diagnosis, explained by the known low FDG avidity of the tumor [19], yet as reported this was not the case here.

The main drawback of this retrospective study was that the small study group consisted of a mixed population of patients with suspected thrombosis on either PET/CT or contrast-enhanced CT. As is generally the rule in clinical practice, one diagnostic procedure is ordered to further evaluate the findings from another diagnostic procedure, and while this report compared PET/CT findings to contrast-enhanced CT, no valid statistical information can be obtained. The encouraging observations reported here, however, that PET/CT detects occult tumor thrombosis and excludes tumor in VTE warrant further prospective evaluation.

As described above, the scans were performed without the addition of intravenous contrast enhancement. However, the CT component of the PET/CT may be optimized by the use of contrast, which could provide reliable characterization and anatomic detail of morphological structures. Combining

acquisition of molecular PET with morphological parameters from contrast-enhanced CT has the potential to optimize PET/CT imaging. When vascular structures are discussed, as in our study, timing of enhanced CT should be directed towards a venous phase (i.e., 50–60 seconds following injection), While some investigators suggested that iodine-containing contrast agents may induce artifacts in the CT-generated attenuation map leading to an erroneous radioactivity distribution on the corrected PET images, others have demonstrated no statistically or clinically significant spuriously elevated standard uptake level as a result of CT iodinated contrast administration [20]. Had the PET/CT scans reported here been performed initially with contrast enhancement, it is likely that no additional correlative imaging would have been necessary to characterize the thrombotic lesions found.

According to CT, tumoral or non-tumoral thrombosis of the vein can be identified but not differentiated from each other, unless hypervascularity is demonstrated in the tumor thrombosis by bolus dynamic contrast-enhanced CT [21,22]. Definitive diagnosis of venous thrombosis by CT is demonstrated by the intraluminal filling defect and focal dilatation of the involved segment of the vein [21,22]. Venous thrombosis produces an intraluminal signal on MRI, which may distinguish tumor thrombus from bland thrombus on the basis of their signal characteristics [23]. According to ultrasonography, tumor thrombosis is demonstrated as echogenic material within the vessel lumen and enlargement of the thrombosed segment, with flow in the thrombus on ultrasound Doppler color scan [24].

In conclusion, PET/CT accurately differentiated tumor thrombosis from benign venous thrombi in our patients. PET/CT appears to be beneficial in the diagnosis of occult tumor thrombosis and may be used as a non-invasive tool to characterize suspicious thrombotic lesions, both above and below the diaphragm, and in the cardiac chambers. By furthering the diagnosis and recognition of tumor thrombi by both imaging and referring physicians, PET/CT may consequently improve patient management. Although this is a limited study, and no valid performance indices for the diagnosis of tumor thrombosis by PET/CT are provided, the findings suggest a potential role for PET/CT in the clinical settings described.

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