Review Article

FLT PET-CT in evaluation of treatment response

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ABSTRACT

Purpose: Review published studies to investigate the value of clinical 3-deoxy-3-^{18}F-fluorothymidine (FLT) positron emission tomography (PET) in predicting response to treatment. **Materials and Methods:** Interrogate databases to identify suitable publications between 2007 and 2013 with a minimum of five patients. Articles within the inclusion criteria were reviewed with major findings reported leading to a descriptive analysis of FLT PET in therapy response. **Results:** Lesions investigated included glioma, head and neck, esophageal, lung, breast, gastric, renal, rectal, sarcomas, germ cell, lymphomas, leukemia, and melanoma resulting in a total of 34 studies analyzed. A variety of therapies were applied and dissimilar PET protocols were widespread making direct comparison between studies challenging. Though baseline, early and late therapy scans were popular particularly in chemotherapy regimes. Most studies investigated showed significantly reduced FLT uptake during or after therapy compared with pretreatment scans. **Conclusion:** Current evidence suggests FLT PET has a positive role to play in predicting therapy response especially in brain, lung, and breast cancers where good correlation with Ki-67 is observed. However, careful attention must be placed in undertaking larger clinical trials where harmonization of scanning and analysis protocols are strictly adhered to fully assess the true potential of FLT PET in predicting response to treatment.

Keywords: ^{18}F-fluorothymidine, positron emission tomography, predict, response, review, treatment

INTRODUCTION

Ability to detect early treatment response has benefit for patients undergoing ineffective therapy particularly where apposite treatment options exist. Potential advantages include fast management changes leading to improved survival with reductions in toxicity and cost of healthcare expenditure from unsuccessful treatment or late possibly less effective 'salvage' therapy regimes. However, limitations with 2-deoxy-2-(^{18}F) fluoro-D-glucose (FDG) positron emission tomography (PET) in treatment response[1,2] promoted investigation of other PET imaging agents.[3] 3-Deoxy-3-^{18}F-fluorothymidine (FLT) as a labeled analogue of thymidine has attracted attention for *in vivo* visualization and quantification of cell proliferation.

Greatly increased cell proliferation is a characteristic of many malignant lesions that may be exploited in FLT PET cancer imaging. Proliferating cells enable thymidine incorporation in DNA synthesis largely during the S-phase of the cell cycle by utilizing the salvage pathway. FLT enters cells via passive diffusion and active nucleoside transporters. It undergoes phosphorylation by the enzyme thymidine kinase 1 (TK1) and it is trapped intracellularly. TK1 activity can increase several fold in proliferating cells compared with those in a resting state. Furthermore malignant cells show overexpression of TK1, that is, higher TK1 activity compared with normal proliferating cells. Despite less than 1% FLT incorporation into DNA there is a correlation between FLT uptake, overexpression of TK1 activity, and cell proliferation. This correlation was confirmed irrespective of cancer type suggesting brain, lung, and breast cancers[4] showed the strongest correlation.

Exploiting the ability of FLT PET in measuring tumor proliferation was forwarded as a tool to predict early treatment response.[5,6] In a time of global fiscal austerity where cancer imaging costs begin to overtake healthcare costs, for example, in USA[7] imaging algorithms with FLT PET may have great potential in managing patient treatment more effectively.

Accordingly this review provides an overall assessment of the role of FLT PET in treatment response through a descriptive analysis of published data. We mention limiting factors associated

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with FLT PET in therapy and suggest recommendations for future implementation.

MATERIALS AND METHODS

A comprehensive literature search using typical databases including PubMed, Medline, etc., was performed on peer-reviewed and published articles involving the use of FLT PET for therapy response in patients. Exclusion criteria included articles outside this remit, articles not published between 2007 and 2013, articles with less than five patients scanned, and articles not in English.

For all studies included in this review the respective full journal publication was interrogated. For each study patient demographics, PET imaging, and acquisition methodology along with tumor type, treatment, therapy regime, and results were collected and recorded.

Accepted publications were reviewed and major findings reported in the results section with a brief summation for each tumor.

RESULTS

A list of 34 FLT PET therapeutic clinical studies from 2007 to 2013 is depicted in Tables 1-6. These illustrate the number of patients (*n*) who underwent all scans in individual protocols, important scan parameters, and Ki-67 correlation status, for example, positive correlation: ✓, no correlation found: ✖, or correlation not attempted: N.a. Hazard ratio (HR) values used to describe risk in survival analysis are reported when performed in studies. Average standardized uptake value (SUV) measurements described in studies were defined as maximum, mean, and peak values (SUV_{max}, SUV_{mean}, and SUV_{peak}, respectively). Statistical significance in studies was assumed for $P \leq 0.05$.

Glioma

Bevacizumab is a humanized monoclonal antibody inhibiting vascular endothelial growth factor (VEGF) used in therapy regimes. Recurrent high-grade glioma has been studied in such regimes integrated with a chemotherapeutic agent irinotecan. One FLT PET study with MRI scanning[8] showed PET scans acquired at 1-2 and 6 weeks posttherapy start yielded lesion FLT SUV_{mean} that predicted overall survival (OS) ($P = 0.006$ and 0.002, respectively) compared with MRI ($P = 0.06$).

This observation was repeated in another similar study.[9] Despite comparable results between imaging modalities the most significant predictor of OS was 6 week FLT PET changes (HR: 10.05, $P < 0.001$) and for progression free survival (PFS) was 6 week FLT uptake (HR: 5.64, $P = 0.001$). In a different dynamic study,[10] again with the same treatment regime high correlation ($r = 0.91$) was observed between FLT tumor uptake and the kinetic parameter influx rate constant (Ki). This result highlighted the potential of simple FLT SUV to monitor treatment response and predict survival characteristics. Elsewhere early kinetic parameter changes[11] enabled patients to be categorized into OS ($P = 0.001$) and PFS ($P = 0.006$) groups with 100 and 88% classification accuracies, respectively. In summation, results from these studies are encouraging and support the potential of FLT for predicting treatment response in glioma with harmonized larger scale clinical trials.

Head and neck cancer

FDG and FLT scans were performed to assess radiotherapy treatment (RT) response in laryngeal cancer.[12] Tumor FDG SUV_{max} and SUV_{mean} were significantly higher ($P = 0.0002$ for both) compared with FLT. Nonetheless tumor-to-background ratios were similar and FLT had potential in monitoring response [Table 2]. Dynamic scanning established SUV_{max} and SUV_{mean} 45-60 min post injection (p.i.) accurately reflected initial FLT uptake[13] with significant decrease between pre and mid 10 Gy of chemoradiation therapy (CRT) in confirmed squamous cell carcinoma (SCC) head and neck patients. Again promise was demonstrated in SCC for predicting outcome to CRT[14] with significant differences in 3-year local control between residual accumulation and no-accumulation groups for posttreatment FLT (HR: 25.57, $P < 0.0001$) and FDG (HR: 6.06, $P = 0.0081$) scans.

Likewise significant FLT SUV_{max} and SUV_{mean} uptake reductions with treatment were seen[15] for oropharyngeal cancer and

Table 1: Glioma FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time (MBq/kg)	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male, F: Female) (years)	Primary cancer	Treatment regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk B: baseline)
Chen *et al.*,	16	2	60 min dynamic (30-60 min sum for ROI) 3D	OSEM 8i 6s	11M, 10F median age: 58 (26-78)	Glioma	Bevacizumab and irinotecan	n.a	B (within 1wk)+ -2wk+6wk post Tx start
Schwarzenberg *et al.*,	27	2	60 min dynamic 3D	OSEM 8i 6s	16M, 11F median age 58	Glioma	Bevacizumab	n.a	B (within 3±2d)+2wk+6wk from Tx start
Schiepers *et al.*,	15	1.5	60 min dynamic 3D	OSEM	6M, 9F mean age 53 (26-76)	Glioma	Bevacizumab and irinotecan	n.a	B+post 1st course (2wk)+Tx end (6wk)
Wardak, *et al.*,	18	2	60 min dynamic 3D	OSEM 6i 16s	8M, 10F Mean 54±15 (26-76)	Glioma	Bevacizumab and irinotecan	n.a	B (within 7d)+2wk+6wk from Tx start

OSEM: Ordered subsets expectation maximization, Bevacizumab: Humanized monoclonal antibody inhibiting vascular endothelial growth factor, irinotecan: Chemotherapy agent, Tx: Treatment, ROI: Region of interest, 3D: Three-dimensional, FLT: 3-deoxy-3-^{18}F-fluorothymidine, PET: Positron emission tomography, n.a: Correlation not attempted

Table 2: Head and neck and esophageal FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male, F: Female) (years)	Primary cancer	Treatmen regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk B: baseline)
Been *et al.*,	10	6 h fast	60 min static	OSEM	M only mean age 68 (54-81)	Head and neck	RT	n.a	B (shortly before Tx)+2-3 months post RT
Menda *et al.*,	7	2.59 MBq/kg 185 max	60 min dynamic 3D	OSEM 2i 8s	6M, 2F; mean age 51.8±8.1 (35-60)	Head and neck	CRT	n.a	B (within 10d mean 3d)+after 5d of Tx
Kishino *et al.*,	26	3.5 MBq/kg 5 h fast	60 min static: 2–3 min/bed 3D	OSEM 2i 8s	25M, 3F mean age 67 (40-83)	Head and neck	CRT	n.a	B+4wk after start+5wk after completion of RT
Troost *et al.*,	10	250	60 min static: 7 min/bed 3D	OSEM 4i 16s	Mean age 61 (52-70)	Head and neck	IMRT/chemotherapy	n.a	B (within 5d, range 0-9d)+2wk+4wk post Tx start
Hoeben *et al.*,	29	250	60 min static: 7 min/bed 2 beds, 3D	OSEM 4i 16s	38M, 10F mean age 60 (39-75)	Head and neck	RT and or chemotherapy	n.a	B+during 2wk+4 wk of treatment
Yue *et al.*,	21	300-400 6 h fast 500 ml H20	56 min (52–82 min) static: 2 min/bed	OSEM	Mean age 60 (45-81)	Esophageal	CRT	n.a	B (within 3d)+2-4 during Tx

FLT: 3-deoxy-3-^{18}F-fluorothymidine, PET: Positron emission tomography, RT: Radiotherapy treatment, CRT: Chemoradiation therapy, IMRT: Intensity-modulated radiotherapy treatment, OSEM: Ordered subset expectation maximization

Table 3: Lung FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male F: Female) (years)	Primary cancer	Treatment regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk B: baseline)
Sohn *et al.*,	28	555	64 min (50-91), static: 5 min/bed 3D	OSEM 2i 16s	5M, 23F median age 58 (40-76)	Lung	Gefitinib	n.a	B (within 1d)+7d post start of Tx
Zander *et al.*,	33	315±83 6 h fast	59±16 min static: 5 min/bed	OSEM	17M, 16F mean age 61 (39-77)	Lung	Erlotinib	n.a	B (within 10d)+1wk and 6wk post Tx start
Mileshkin *et al.*,	50	259	60±15 min static: scans within 5 min of B	MANY	30M, 21F median age 61 (47-78)	Lung	Erlotinib	n.a	B+14d+56d (±3d) post Tx start
Kahraman *et al.*,	22	305±89 6 h fast	58±15 min static: 5 min/bed	OSEM 4it 16s	13M, 17F median age 64 (39-79)	Lung	Erlotinib	n.a	B (within 10d)+1wk+6wk from Tx start
Kobe *et al.*,	22	311±91 6 h fast	57±13 min static: 5 min/bed	OSEM 4i 16s	13M, 17F median age 64 (39-79)	Lung	Erlotinib	n.a	1wk+6wk post Tx start
Yang *et al.*,	68	300-400 6 h fast	60 min static: 4 min/bed	OSEM 2i 28s	48M, 20F median age 61 (36-84)	Lung	Surgery	✓	Pre surgery
Scheffler *et al.*,	40	300 6 h fast	60 min static: 5 min/bed 6 beds	OSEM	19M 21F mean age 62 (38-78)	Lung	Erlotinib	✖	B (within 9d)
Saga *et al.*,	20	300	50 min static: 3 min/bed 3D	OSEM	11M 9F mean age 73 (58-85)	Lung	Carbon-ion RT	n.a	B+3 month post Tx end

FLT: 3-deoxy-3-18F-fluorothymidine, PET: Positron emission tomography, gefitinib and erlotinib: Tyrosine kinase inhibitor drugs, OSEM: Ordered subset expectation maximization, ✓: Positive correlation, ✖: No correlation found, n.a.: Correlation not attempted, 3D: Three-dimensional

Table 4: Breast FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male, F: Female) (years)	Primary cancer	Treatment regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk, B: Baseline)
Kenny *et al.*,	13	153-381	95 min dynamic	FBP	F only mean age 54 (36-80)	Breast	FEC chemotherapy	n.a	B (repeated within 2-8d)+1 wk post start Tx
Contractor *et al.*,	20	210±8	66.5 min dynamic	FBP	Mean age 54 (41–69)	Breast	Docetaxel	n.a	B+2wk after 1 or 2 cycles of Tx
Lubberink *et al.*,	14	370	60 min dynamic 2D	FBP+OSEM 2i 16s	Not given	Breast	Chemotherapy	n.a	B (within 1d range: 0-9d)+after 1st cycle of Tx

FLT: 3-deoxy-3-18F-fluorothymidine, PET: Positron emission tomography, FBP: Filtered-backprojection, Docetaxel: Taxane chemotherapy agent, FEC: 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy, OSEM: Ordered subset expectation maximization, n.a.: Correlation not attempted

intensity-modulated RT (IMRT) with or without chemotherapy. Equally one study[16] during the first 2 weeks of various RT regimes with or without cisplatinum for SCC showed significant reductions in FLT $SUV_{max} \geq 45\%$ ($P = 0.035$) and in visually defined gross tumor volume (GTV_{vis}) ≥ median ($P = 0.037$) that agreed with improved 3 year disease free survival (DFS). Moreover improved 3 year locoregional control was seen with significant GTV_{vis} decrease ≥ median ($P = 0.021$) in the 4th week of treatment. In summation, results from these studies are encouraging and support the potential of FLT for predicting

Table 5: Gastric, renal, rectal, and sarcoma FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male, F: Female) (years)	Primary cancer	Treatment regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk, B: baseline)
Ott *et al.*,	37	Mean: 300 (270-340) 6 h fast	≥45 min dynamic 8 min/bed, 2D	OSEM 4it 8s	31M, 14F Median age 61 (36-78)	Gastric	Neoadjuvant	×	B+2 wk from Tx start
Liu *et al.*,	16	185-555	dynamic 30 min+static 60 min 2D	OSEM	12M, 4F Median age 60 (42–76)	Renal+other solid malignancy	Sunitinib	n.a	B+during Tx+after sunitinib withdrawal within 1 cycle
Wieder *et al.*,	10	300	60 min static: 8 min/bed Dynamic, 2D	FBP	7M, 3F Mean age 65±13	Rectal	Neoadjuvant CRT	n.a	B+2 wk after start+3-4 wk post Tx end presurgery
Dehdashti *et al.*,	14	337±63 pre Tx 300±115 post Tx	45-60 min Static Saline: 0.5-1 L	OSEM	12M, 2W Mean age 54 (39–75)	Rectal	Neoadjuvant CRT	n.a	B+2 wk post Tx start
Been *et al.*,	10	Pre: 399 (320-430) Post: 363 (120–430)	60 min static: 5 min/bed	OSEM	6M, 4F; Mean age 51 (27–71)	Sarcoma	HILP	n.a	B+39d (28–49d range) post perf
Benz *et al.*,	20	Mean: 246±19 (211-300)	60 min i.v. contrast CT 6 h fast, static, 3D	OSEM 2i 8s	9M, 11F Median age 62 (26–94)	Sarcoma	Neoadjuvant	×	B (within 7d±8.7)+13.6d (±9.3d) from Tx end

FLT: 3-deoxy-3-18F-fluorothymidine, PET: Positron emission tomography, FBP: Filtered-backprojection, OSEM: Ordered subset expectation maximization, 2D: Two-dimensional, 3D: Three dimensional, CT: Contrast tomography, Sunitinib: Vascular endothelial growth factor receptor tyrosine kinase inhibitor, HILP: Hyperthermic isolated limb perfusion, i.v.: Intravenous

Table 6: Germ, lymphoma, leukemia, and melanoma FLT PET therapy studies

Author [reference]	*n*	FLT MBq+fast time	Uptake time+PET acquisition factors	Image recon	Demographic (M: Male, F: Female) (years)	Primary cancer	Treatment regime (Tx)	Ki-67 cor	FLT scan regime (d: day, week: wk, B: baseline)
Pfann'berg *et al.*,	10	350-400 6 h fast	60 min, 3D static: 3 min/bed Neg. oral contrast	OSEM 2it 8s	M only Mean age 38 (23-48)	Germ cell	Chemotherapy	×	B+post 1 cycle+3wk post Tx end
Herrmann *et al.*,	22	mean: 300 (270-340)	45 min static	FBP	16M, 6F Mean age 59±14	Lymphoma high grade NHL	R-CHOP/ CHOP, rituximab	n.a	B (within 1wk); Group 1: 1wk+6wk post R-CHOP/ CHOP; Group 2: 2d after ritux. +2d after CHOP.
Herrmann *et al.*,	66	mean: 300 (270-340)	45 min static	FBP	38M, 32F Median age 63 (26-82)	Lymphoma aggressive NHL	R-CHOP	×	B (within 4d)
Herrmann *et al.*,	5	Mean: 300 (270-340)	45 min static	FBP	4M, 3F Mean age 71 (47-87)	Lymphoma mantle cell	Various systemic	✓	B (within 7d)+6d (±1d) from 1st course Tx start
Vanderhoek *et al.*,	8	185	45 min static: 10 min/bed	OSEM 2i 28s	6M, 2F 19-70	Leukaemia	Induction chemotherapy	n.a	B+multiple time points during Tx
Ribas *et al.*,	9	7.8 MBq/kg Mean: 196±10%	45-60 min static 3D	Not given	7M, 2F Mean age 57 (range: 27-81)	Melanoma	Tremelimumab	n.a	B+post Tx at 61d (43-98d)
Aarntzen *et al.*,	9	250	60 min static	OSEM	M+F 18-75	Melanoma	Dendritic cell vaccine	n.a	Various time points post vaccination

FLT: 3-deoxy-3-18F-fluorothymidine, PET: Positron emission tomography, FBP: Filtered-backprojection, CHOP: Cyclophosphamide-adriamycin-vincristine-prednisone chemotherapy, rituximab: monoclonal anti-CD20 antibody, R-CHOP: Rituximab-CHOP, tremelimumab: CTLA4-blocking antibody, n.a.: Correlation not attempted, NHL: Non-Hodgkin's lymphoma

treatment response in head and neck cancer with harmonized larger scale clinical trials.

Esophageal cancer

Proliferative change was observed in esophageal SCC with RT[17] where patients experiencing delays in treatment exhibited apparent accelerated repopulation.[18] FLT also showed potential in monitoring bone marrow proliferation reduction with treatment (no proliferation seen at 10 Gy) along with promise of differentiating between residual disease and esophagitis. In summation, more work is required to establish the potential of FLT PET in esophageal cancer.

Lung cancer

FLT PET-CT has been applied most often where cancer growth blocking tyrosine kinase inhibitor drugs, for example, gefitinib and more recently erlotinib were used [Table 3].

In non-small-cell lung carcinoma (NSCLC) advanced adenocarcinoma patients demonstrated significant FLT PET SUV_{max} reduction at 7 days following the start of gefitinib[19] that predicted responders from nonresponders ($P < 0.001$) by CT as did percentage changes in SUV_{max} ($P < 0.001$). Elsewhere FLT scans after 1 week of erlotinib therapy predicted significantly prolonged PFS (HR: 0.31, $P = 0.04$) in NSCLC.[20] In contrast early FDG PET

response predicted significantly longer PFS (HR: 0.23, $P = 0.002$), OS (HR: 0.36, $P = 0.04$) and non-progression following 6 weeks of therapy ($P = 0.02$). Again with NSCLC erlotinib therapy[21] PET showed partial metabolic response (PMR) at days 14 and 56 positively correlated with improved PFS with FDG and FLT. Conversely, only FDG PET day 14 PMR was significantly associated with improved OS (HR: 0.44, $P = 0.03$).

Similarly another study[22] utilizing different SUV showed FDG and FLT scans predicted PFS after 1 week of erlotinib irrespective of SUV used. FDG SUV at 1 week was more reliable for predicting early response, while 1 week FLT and 6 week FDG PET metabolic volume estimations had potential for response prediction. Furthermore short-term outcome to erlotinib in NSCLC could be predicted using a variety of SUV measurements[23] derived from 1 and 6 week residual FDG uptake ($P < 0.05$). Improved PFS was reflected in low residual FDG and FLT uptake observed early and late respectively during treatment. It was established FLT SUV_{max} significantly correlated with both Ki-67 staining and microvessel density (MVD) ($r = 0.550$ and 0.633; $P = 0.000$ and 0.000, respectively) measured with a monoclonal antibody (CD105-MVD).[24] Those subjects with lower rather than higher CD105-MVD had longer median survival times ($P = 0.046$) enabling prediction of response to antiangiogenic therapy. More recently[25] baseline FDG and FLT SUV_{max} <6.6 and <3, respectively were shown to be prognostic indicators (HR: 4.3, $P < 0.001$ and HR: 2.2, $P = 0.027$, respectively) correlating significantly with longer survival in metastatic NSCLC treated with erlotinib.

On the other hand FLT PET-CT has also been investigated with carbon ion RT due to potential advantages in dose distribution and relative biological effectiveness over conventional RT. In a NSCLC study[26] baseline FLT SUV_{max} <3.7 acted as a significant prognostic indicator for both PFS ($P = 0.003$) and for cause-specific survival ($P = 0.002$). Though posttreatment uptake was complicated by the presence of radiation pneumonitis. Results from these studies are encouraging and support the potential of FLT for predicting treatment response in lung cancer with harmonized larger scale clinical trials.

Breast cancer

Dynamic FLT PET in breast cancer was investigated as a prognostic indicator[27] with high reproducibility seen in serial baseline scans (test-retest $r \geq 0.97$). Decreased uptake 1 week after combination 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy distinguished between complete response (CR), partial response (PR), and stable disease (SD) using changes in SUV at 90 min p.i. ($P = 0.022$) and K_i ($P = 0.022$) [Table 4].

A different study performed kinetic scans at baseline and 2 weeks after starting the first or second cycle of docetaxel.[28] Familiar significant reductions were again seen in FLT SUV_{max} and SUV_{mean} here normalized to body surface area ($P = 0.0002$ and 0.0003, respectively), while mid therapy lesion response was predicted by significant reduction in tumor SUV_{mean} ($P = 0.004$).

In another dynamic study,[29] FLT scans were performed prior to and after the first cycle of chemotherapy in locally advanced disease. Authors concluded tumor-to-whole blood ratio measurements exhibited less bias compared with SUV and accordingly were preferred for treatment response assessment.

An example of FLT PET breast cancer imaging during therapy is illustrated in Figure 1 showing significant SUV_{max} reduction (>39%) pretherapy (lower row images) versus 10 days after FEC chemotherapy start (upper row images). Sections shown depict the lesion FLT maximum uptake in each case with the lesion circled for identification. This patient had an excellent clinical response. Results from these studies are encouraging and support the potential of FLT for predicting treatment response in breast cancer with harmonized larger scale clinical trials.

Gastric cancer

FDG and FLT PET were used to image gastric cancer at baseline and 2 weeks following chemotherapy start.[30] FLT SUV_{mean}

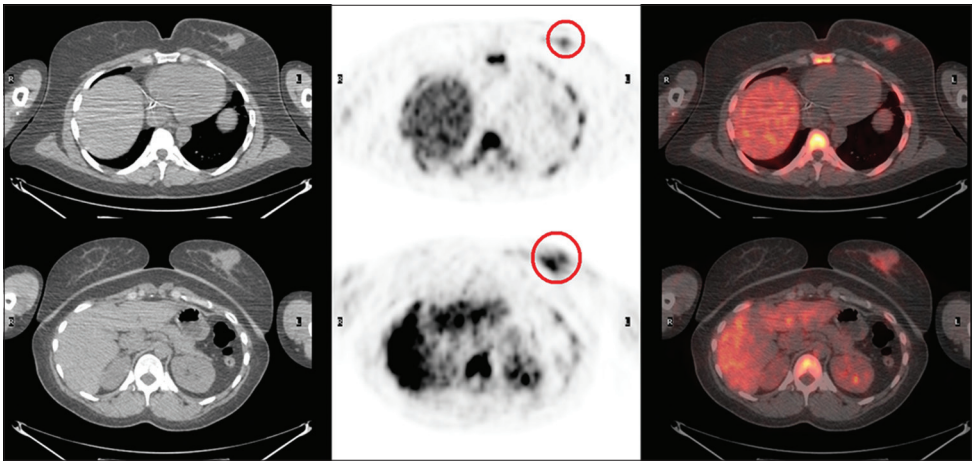

Figure 1: Breast FLT PET-CT SUV_{max} reduction >39% pretreatment (lower row) compared with 10 days after start of the first cycle of chemotherapy (upper row). Drawn circles indicate lesion position on respective PET slices containing SUV_{max}. FLT = 3-Deoxy-3-^{18}F-fluorothymidine, PET = positron emission tomography, CT = computed tomography, SUV = standardized uptake value, max = maximum

reduced from 6.0 to 4.2 between baseline and 2 weeks scans, respectively. It was concluded poor prognosis was only associated with day 14 higher FLT SUV_{mean} (HR: 1.53, $P = 0.048$) using a Martindale plot and with Ki-67 (HR: 0.97, $P = 0.006$) [Table 5]. Authors suggested the observation of relatively high proliferation and poor prognosis 2 weeks following therapy start may reflect chemoresistance. More work is required to establish the potential of FLT PET in gastric cancer.

Renal cancer

FLT PET scans were performed with renal cell cancer and other solid malignancies at baseline, during, and then one cycle after sunitinib withdrawal.[31] It was proposed significant SUV_{mean} increase ($P = 0.047$) during withdrawal reflected VEGF receptor tyrosine kinase inhibitor withdrawal flare. Those with larger flare benefited least suggesting potential for predicting response to therapy. More data is required to establish the potential of FLT PET in renal cancer.

Rectal cancer

Dynamic FLT PET scans in rectal cancer[32] also showed significant decrease in tumor SUV_{mean} between baseline and after 2 weeks CRT start ($P < 0.005$) with an additional decrease for the preoperative scan ($P = 0.005$). Changes observed however were not predictive of treatment response.

In another CRT study,[33] pretherapy staging FDG, baseline FLT PET, and 2 week posttherapy start FLT scans were performed. Pretherapy lesion SUV_{max} from FLT and FDG scans were 6.1 ± 1.9 and 17.3 ± 12.7, respectively; while during therapy FLT SUV_{max} was 2.6 ± 1.2. However, the percentage change in FLT SUV_{max} during therapy for responders versus nonresponders was not significant (58.0 ± 22.9 vs $56.1 \pm 23.3\%$, $P = 0.40$).

Authors demonstrated significantly improved DFS was equally predicted by high pretherapy FDG ($SUV_{max} \geq 14.3$), low during therapy FLT ($SUV_{max} < 2.2$), and high percentage change in FLT uptake (≥60%); with $P < 0.05$ for all values, respectively. More work is required to establish the potential of FLT PET in rectal cancer.

Soft tissue sarcoma

FLT PET was used to assess response in advanced soft tissue sarcomas with hyperthermic isolated limb perfusion (HILP)[34] where once more lesion SUV_{max} and SUV_{mean} reductions following therapy were significant ($P = 0.0008$ and 0.002, respectively). Pre HILP and high SUV_{mean} correlated significantly albeit weakly with % necrosis after HILP ($r = 0.64$, $P < 0.05$); suggesting improved response with initially high uptake lesions. Similarly another study,[35] revealed a significant reduction in SUV_{peak} between baseline and after neoadjuvant therapy ($P < 0.001$) that significantly correlated with tumor size change ($r = 0.52$; $P = 0.02$) and with tumor necrosis ($r = -0.68$; $P = 0.001$). In contrast, uptake changes did not predict histopathological response nor did after therapy FLT uptake reflect TK1 or Ki-67 staining. More work is required to establish the potential of FLT PET in soft tissue sarcoma.

Germ cell tumor

FDG and FLT PET scans were performed with chemotherapy in germ cell cancer,[36] confirming lesion SUV_{max} and SUV_{mean} decreased jointly after one cycle and after treatment using both tracers. However, this was without significance for distinguishing responders from nonresponders. Moreover FLT uptake did not significantly correlate with Ki-67 staining [Table 6]. The authors' conjecture this may possibly be interpreted a consequence of the inhomogeneous pathology of this disease where lesions can be composed of different histological layers having disparate proliferation characteristics. More work is required to establish the potential of FLT PET in germ cell cancer.

Lymphoma

In non-Hodgkin's lymphoma (NHL), FLT scans[37] showed a significant decrease in lymphoma SUV_{mean} compared with baseline, at 1 week ($P < 0.001$) and 6 weeks ($P = 0.003$) in one group imaged following treatment with cyclophosphamide-adriamycin-vincristine-prednisone (CHOP) chemotherapy with or without rituximab immunotherapy (R-CHOP). This result was replicated in a second group 2 days after CHOP ($P = 0.004$), but conversely was not true for rituximab used alone in the treatment regime. Similarly, this researcher investigated FLT PET prior to R-CHOP therapy in aggressive B-cell NHL[38] reporting initial lesion SUV_{mean} significantly lower for those achieving CR compared with non-CR ($P = 0.049$). SUV_{max} and SUV_{mean} were also significantly lower ($P = 0.002$ and 0.012, respectively) in patient subgroups designated low risk compared with high risk defined by the International Prognostic Index (IPI) for survival of diffuse large B-cell lymphoma.

Furthermore, the same researcher studied FDG and FLT PET in mantle cell lymphoma[39] prior to treatment, while then performing repeat FLT scans 6 days after the start of immunochemotherapy. A 44 and 45% familiar decrease in FLT SUV_{max} and SUV_{mean}, respectively was observed 1 week after therapy start. Immunohistochemistry was performed in all PET positive patients based on the initial staging and the Ki-67 positive lymphoma cells score varied from 1 to 85%. Analysis showed a strong positive correlation between higher initial FLT uptake and higher Ki-67 proliferation ($r = 0.91$) suggesting potential for response monitoring. The results from these studies are encouraging and support the potential of FLT for predicting treatment response in lymphoma with harmonized larger scale clinical trials.

Leukemia

FLT PET was applied to acute myeloid leukemia at different time points (pretherapy and days 2, 4, 5, and 6 posttherapy) using bone marrow uptake analysis.[40] FLT SUV_{max} and SUV_{mean} were 0.8 and 3.6 for CR and 1.6 and 11.4 for resistant disease, respectively. Differences were statistically significant ($P < 0.001$) and independent of time point assessment suggesting potential to distinguish these clinical response groups as early as day 2 after therapy start. More work is required to establish the potential of FLT PET in leukemia.

Melanoma

FDG and FLT PET scanning were performed on patients with advanced disease pre and post anti-CTLA4 antibody tremelimumab treatment.[41] Significant increasing FLT SUV_{max} and SUV_{mean} in the spleen were demonstrated ($P = 0.015$ and 0.018, respectively), confirming proliferation changes in secondary lymphoid tissue posttreatment can be detected with this therapy regime. FLT PET scans to assess anticancer vaccination were performed on patients with regional lymph node (LN) metastases following intranodally injected dendritic cell (DC) vaccine therapy[42] at various time points following vaccination.

Authors speculated successful vaccination results in significantly increased proliferation of activated lymphocytes in proximal LNs allowing assessment of vaccine induced T and B cell immune cell responses. A significant increase was shown in LN SUV_{max} ($P < 0.05$) for patients receiving additional intranodal vaccinations compared with controls. Results show promise for FLT PET to monitor increased proliferation to distinguish responders from nonresponders for vaccine therapy in cancer. However, more work is required to establish the potential of FLT PET in melanoma.

DISCUSSION

Some studies achieved treatment response prediction derived solely from baseline scans, for example, lung[25,26] and NHL.[38] The vast majority of studies required statistically significant tumor uptake or metabolic volume parameters derived from combinations of baseline, during, and posttherapy scans to achieve this. However, there were exceptions, for example, using chemotherapy in germ cell cancer[36] possibly due to low adenosine triphosphate levels in GCT metastases.[43] Complex interactions possibly between neoadjuvant treatments with tissue in rectal cancer[32] were also proposed. Alternatively, multiple reasons were speculated by the author for failing to predict response in neoadjuvant treated sarcomas.[35] Furthermore, in many studies comparing FDG with FLT PET we see the complimentary nature of both tracers exhibited together rather than significant domination by either. Again there are exceptions, for example, in laryngeal cancer with RT[12] who questioned the value of both tracers.

Future routine general clinical use of FLT PET must be supported by robust repeatability and reproducibility data. This was corroborated using uptake and metabolic volume investigations in breast cancer[27] and NSCLC;[44-46] validating further studies using FLT.

In contrast, possible inconsistency using FLT PET to monitor tumor proliferation may arise from other reasons. For example uptake that is not solely driven by TK1, but includes other complex and competing factors such as endogenous thymidine, degrading metabolism of phosphorolated metabolites, DNA repair rates, and transport via human equilibrative nucleoside transporters (hENT)[47-50] showed different transport mechanisms, that is, hENT1 and hENT1 dominated by passive diffusion influenced uptake of thymidine analogues[3] H-thymidine and ^{3}H-FLT, respectively in a human adenocarcinoma cell line. Those authors found difficulty in characterizing the relative importance between hENT1 and TK1 in dominating uptake and observed tracer concentrated in nonproliferating tumor cells, due to lower levels of TK1, which might have influence in PET studies.

We see a vast diversity in study protocols investigated. Limited patient numbers completed their full scan regime with treatment, for example, minimum of five mantle cell lymphoma subjects[39] to a maximum of 68 subjects with NSCLC[24] leading to potential for underpowered studies. FLT injected activity regimes ranged from 153 MBq (4.14 mCi) in breast cancer[27] to 555 MBq (15 mCi) in lung cancer[19] with variation in p.i. uptake times prior to scanning (30-90 min) along with dynamic, kinetic, and static imaging configurations. Two-dimensional (2D) and 3D scan protocols were observed while emission acquisition time per bed varied from 2[17] to 10 min[40] and image reconstruction techniques included filtered-backprojection (FBP) and ordered subset expectation maximization (OSEM). Moreover scan timing in sequential imaging studies during therapy exhibited considerable variation for pretreatment scan time, for example, 1 day[19] compared with 10 days[22] and similarly with imaging posttreatment. Similar to FDG studies a number of publications utilized fasting prior to FLT scanning[12,22,20,36] presumably to improve FLT uptake; though this is unproven.

We also observed an assortment of data analysis techniques, for example, SUV_{max}, SUV_{mean}, SUV_{peak}[30,35,42] and uptake derived lesion volume estimates[22] to investigate outcome correlations. Importance of image analysis parameters was addressed with FLT PET in solid malignancies[51] to reveal that choice of region of interest (ROI) influences both SUV_{peak} and tumor response. Careful consideration should be taken in evaluating the efficacy of these factors for quantifying treatment response.

Accordingly we advocate a more unified approach towards application of FLT PET in evaluating treatment response. In the USA PET Response Evaluation Criteria in Solid Tumours (PERCIST) was proposed to standardize FDG PET functional response assessment.[52] Similarly in Europe guidelines[53] provide a minimum standard for acquisition and interpretation of FDG PET for tumor imaging focusing on optimization of diagnostic quality and quantification. Future, larger scale and adequately powered multicenter trials adopting such standards may provide a clinical evidence base of the true value of FLT PET in response monitoring. Thereby having potential to reduce bias in PET systematic reviews[54] and assisting in promoting the best current imaging strategy for the patient's welfare.

In some cases, FDG and FLT scans were performed on the same subject in studies. Under these circumstances favorable FDG results were included in this review for comparison to highlight potential advantages or disadvantages of using FLT in therapy

response. It has been intimated FDG may be advantageous for monitoring cytotoxic effects arising from cell death,[55] while FLT may be beneficial for examining cytostatic responses.[56] Similar interest was expressed in a multifaceted investigational approach, for example, through studying the association of FLT PET uptake with other tumor dependent characteristics, for example, hypoxia, angiogenesis, apoptosis[57,58] or MVD[24] etc., which is not yet fully established clinically.

With inclusion of other scanning modalities such comprehensive integrated molecular imaging strategies may succeed in developing personalized oncology[59] potentially to optimize outcome thereby overcoming current restricted 'one hat fits all' treatment policies. Despite concerns over FLT production/yield/cost, relatively low uptake, and surrogate proliferation status[60] evidence suggests FLT PET has a role to play within such a multi-focused functional imaging framework for monitoring tumor response. However, further work is required for full validation of PET tumor proliferation imaging with this labeled pyrimidine.[61]

CONCLUSION

FLT PET in the context of treatment management is currently works in progress with real need for harmonization in future investigations. However, the evidence to date suggests promise for this proliferation tracer especially for brain, lung, and breast cancers where strong correlation with Ki-67 is observed. Larger scale multicenter trials are recommended to investigate the true potential of FLT in the treatment response pathway.

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