



Review

A systematic review on [¹⁸F]FLT-PET uptake as a measure of treatment response in cancer patients



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Received 10 November 2015; accepted 15 November 2015

Available online 25 January 2016

KEYWORDS

Positron-emission tomography;
3'-Deoxy-3'-(¹⁸F) fluorothymidine;
Alovudine;
Cell proliferation;
Neoplasms;
Chemotherapy;
Radiotherapy;
Chemoradiotherapy;
Imaging biomarker

Abstract Imaging biomarkers have a potential to depict the hallmarks of cancers that characterise cancer cells as compared to normal cells. One pertinent example is 3'-deoxy-3'-¹⁸F-fluorothymidine positron emission tomography ([¹⁸F]FLT-PET), which allows non-invasive *in vivo* assessment of tumour proliferation. Most importantly, [¹⁸F]FLT does not seem to be accumulating in inflammatory processes, as seen in [¹⁸F]-fludeoxyglucose, the most commonly used PET tracer for assessment of cell metabolism. [¹⁸F]FLT could therefore provide additional information about the tumour biology before, during and after treatment. This systematic review focuses on the use of [¹⁸F]FLT-PET tumour uptake values as a measure of tumour response to therapeutic interventions. The clinical studies which evaluated the role of [¹⁸F]FLT-PET as a measure of tumour response to treatment are summarised and the evidence linking [¹⁸F]FLT-PET tumour uptake values with clinical outcome is evaluated.

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1. Introduction

Positron emission tomography (PET) has become an essential component of cancer imaging and management of cancer patients over the past 10–15 years. PET imaging is a physiological imaging technique that depends on tumour pathophysiology and metabolic processes [1]. The distinctive properties of PET imaging agents (e.g. [^{18}F]-fludeoxyglucose [^{18}F]FDG] reflecting glucose metabolism, 3'-deoxy-3'- ^{18}F -fluorothymidine [^{18}F]FLT] being a marker for tumour cell proliferation and various other tracers for imaging of other cancer hallmarks) allow spatial detection and localisation of the pathophysiological processes [2,3]. Therefore, information rendered from PET images can serve as an indicator of response to treatment which affect these processes. Thus, PET imaging agents can serve many unique purposes, such as patient stratification, eligibility confirmation, disease progression, response assessment and prediction of clinical outcomes.

Response assessment in solid tumours is usually performed using size criteria derived from computed tomography (CT) scans [4]. Vigorous discussion has confronted the use of anatomic assessments alone, primarily as it may take several weeks to notice any reduction in tumour size. Moreover, only morphological information can be attained, and this may not be suitable to assess early treatment response. Furthermore, novel targeted therapies may not even lead to tumour shrinkage despite having a beneficial effect on patient outcome. These limitations made clinicians concentrate more on functional and molecular imaging techniques such as PET imaging using specific tumour metabolic tracers [5]. Measurement of functional imaging biomarkers compared to mere morphological evaluation may allow for more accurate evaluation of various cancer types and their development through time.

The most commonly used PET tracer in oncology is [^{18}F]FDG for measuring tumour glucose metabolism [6]. [^{18}F]FDG is a glucose analogue and is phosphorylated by hexokinase, but cannot undergo further metabolism in the glycolytic pathway [7]. Hence, the degree of [^{18}F]FDG uptake detected by the PET scanner reflects the level of glucose metabolism. The specificity of [^{18}F]FDG-PET may decrease in the presence of [^{18}F]FDG-avid treatment-induced inflammation surrounding the tumour. This occurrence may hamper the interpretation of [^{18}F]FDG-PET scans as [^{18}F]FDG uptake in activated inflammatory cells may lead to overestimation of the percentage viable tumour cells and depreciating the feasibility of observing an early metabolic response [8].

To improve the accuracy of early PET assessment and the accuracy of target delineation, [^{18}F]FLT has been introduced for imaging tumour cell proliferation [1]. [^{18}F]FLT is monophosphorylated by thymidine kinase 1 (TK1), which leads to intracellular trapping.

Since the activity of TK1 is elevated during the S phase of the cell cycle, [^{18}F]FLT-PET uptake reflects tumour cell proliferation. Hence, there is a good probability that persistent [^{18}F]FLT-PET uptake after the first cycle of treatment would mean that the drug either did not reach its target or was ineffective. Thus, [^{18}F]FLT-PET is very likely to become a 'drug terminator' helping drug developers to eliminate ineffective compounds in the early phase clinical trials [5].

Quantifying tumour proliferation using [^{18}F]FLT-PET has several advantages: primarily, it is non-invasive procedure, [^{18}F]FLT-PET generates three-dimensional tumour images and multiple tumour sites can be measured simultaneously and repeatedly [9]. Moreover, [^{18}F]FLT-PET is capable of evaluating whole tumour proliferation heterogeneity, which is not possible in biopsy specimens, and it is clinically feasible in day-to-day practice [10]. Therefore, the purpose of this review is to investigate the clinical value of [^{18}F]FLT-PET proliferative imaging for prediction of response to treatment. This will further allow clinicians to better understand the tumour metabolic processes and thereby select specific drug agents or treatment strategies which precisely targets key metabolic pathways.

2. Materials and methods

2.1. Search strategy

To identify all relevant publications, we performed systematic searches in the bibliographic databases EMBASE.com and the Cochrane Library (via Wiley) from inception to 1st September 2015. Search terms included controlled terms from EMtree in EMBASE.com as well as free-text terms. We used free-text terms only in the Cochrane Library (see supplemental data). Search terms expressing 'FLT-PET' were used in combination with search terms comprising 'neoplasms'. The references of the identified articles were searched for relevant publications.

2.2. Selection process

Two reviewers (VRB and GMK) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full-text article was checked for the eligibility criteria. Differences in judgement were resolved through a consensus procedure.

Studies were included if they met the following criteria:

- (i) The study investigated the performance of [^{18}F]FLT-PET/CT or PET for evaluating treatment response in oncological patients;
- (ii) Patients underwent chemotherapy, chemoradiotherapy or radiotherapy; and
- (iii) Clinical outcome was assessed.

We excluded studies if they were:

- (i) Animal or *in vitro* studies;
- (ii) Studies on investigational drugs;
- (iii) Not available in full text or not written in English; and
- (iv) Certain publication types: reviews, editorials, letters, legal cases, interviews, case reports, and comments.

3. Results

3.1. Search results

The literature search generated a total of 967 references: 949 in [EMBASE.com](#) and 18 in the Cochrane Library. After removing duplicates of references that were selected from more than one database, 935 references remained. The flow chart of the search and selection process is presented in [Fig. 1](#). Out of 935, only 35 were considered as eligible. [Table 1](#) includes a summary of clinical studies and their outcome in various tumour types based on [¹⁸F]FLT-PET/CT proliferative imaging.

3.2. Systemic therapy

Recently, [¹⁸F]FLT-PET is drawing attention as an early predictor of tumour response. The predictive value of pre-treatment [¹⁸F]FLT-PET imaging in aggressive non-Hodgkin's lymphoma (NHL) cancer patients (n = 62) treated with standard cyclophosphamide, doxorubicin, vincristine and prednisolone with rituximab (R-CHOP) regimen was evaluated by Herrmann et al. [11]. Pre-treatment [¹⁸F]FLT-PET scans showed a lower mean standardised uptake value (SUVmean) for those achieving complete response compared with non-complete response (p = 0.049). Another study by this group (n = 54) [12] showed that reduction of [¹⁸F]FLT SUVmean/mean maximum standardised uptake values (SUVmax) 1 week after the start R-CHOP was significantly larger in patients reaching complete response (p < 0.006). Change in SUV was also inversely correlated with survival and showed a hazard ratio of 0.65 per point increment of [¹⁸F]FLT SUVmean. These results are in accordance with findings from Lee et al. [13]

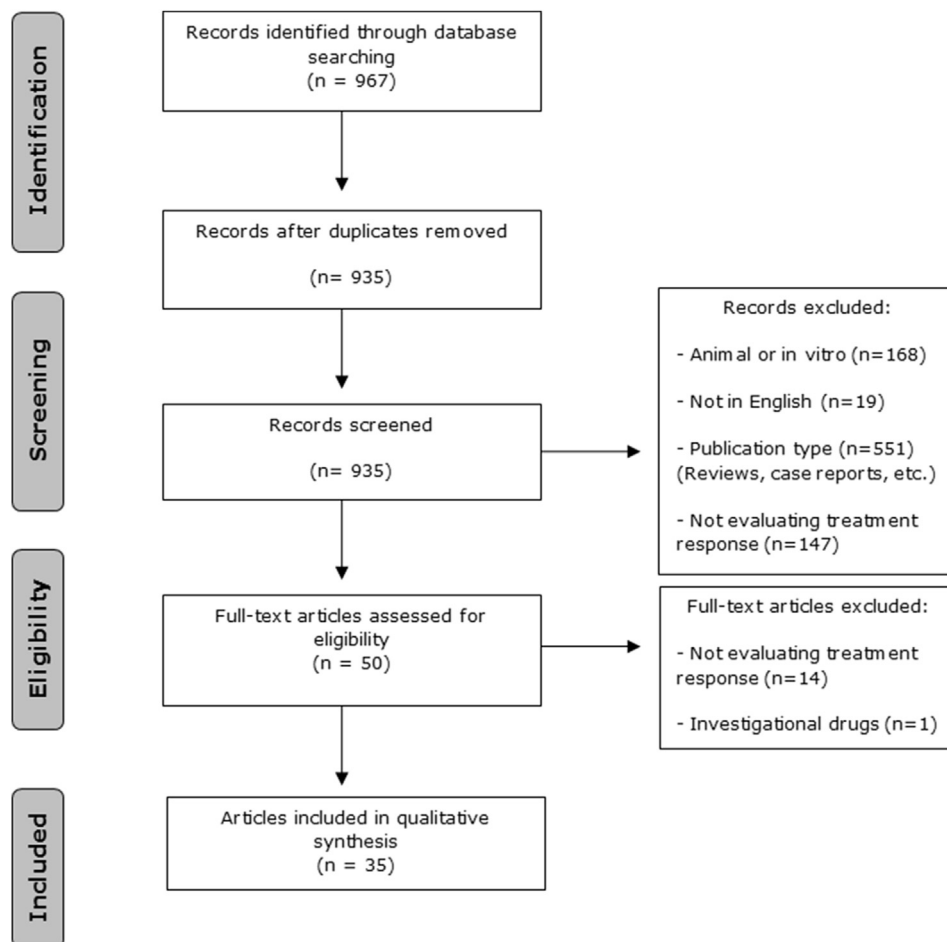


Fig. 1. Flowchart of the search and selection procedure of studies.

Table 1
Summary of clinical studies and their outcomes in various tumour types based on [¹⁸F]FLT-PET proliferative imaging.

No. of patients	Tumour type	Treatment type	Clinical study	Purpose	Results	Conclusion(s)	Reference
20	Breast cancer	CTx	Relationship between change in [¹⁸ F]FLT-PET uptake and clinical response.	To establish whether early changes in [¹⁸ F]FLT-PET can predict clinical response to docetaxel therapy in breast cancer.	Docetaxel treatment resulted in a significant decrease in [¹⁸ F]FLT uptake for both SUV _{max} and SUV _{mean} at 60 min. Decrease in [¹⁸ F]FLT uptake was significantly larger in responders compared to non-responders (40.2% versus 10.5% resp.). A >20% reduction SUV _{mean} was associated with target lesion size changes and response after three cycles (0.85 sensitivity and 0.80 specificity).	Changes in [¹⁸ F]FLT-PET early after initiating docetaxel chemotherapy are associated with target lesion response mid-therapy.	[22]
14	Breast cancer	CTx and hormonal therapy	Change in [¹⁸ F]FLT uptake and correlation with response to treatment	To determine the whether [¹⁸ F]FLT-PET is useful in the monitoring of breast cancer therapy, as compared with [¹⁸ F]FDG-PET and to assess the value of [¹⁸ F]FLT-PET in predicting long-term clinical outcome.	Change in [¹⁸ F]FLT uptake after one cycle of chemotherapy are correlates with late changes in tumour size and change in CA 27.29 tumour marker levels (respectively p = 0.01 and p = 0.001).	[¹⁸ F]FLT uptake after one cycle of chemotherapy is correlated with changes in tumour size and tumour marker levels. Therefore, [¹⁸ F]FLT may be useful in predicting long term clinical outcome of breast cancer.	[23]
13	Breast cancer	CTx	Relationship between change in [¹⁸ F]FLT parameters and treatment response.	To define whether [¹⁸ F]FLT-PET can be used to quantify early response of breast cancer to chemotherapy.	Decreases in Ki and SUV (at 90 min) 1 week after treatment discriminated between clinical response and stable disease (p = 0.022 for both parameters). Responding lesions had an average decrease in [¹⁸ F]FLT-PET of 41.3% and 52.9% for SUV ₉₀ and Ki, respectively. In non-responding lesions, there was an average increase in both variables.	[¹⁸ F]FLT-PET is able to distinguish patients with stable disease and those with CR/PR 1-week post-treatment.	[2]
53	HNSCC	RT or CHRT	Correlation between baseline [¹⁸ F]FLT uptake and response to treatment.	To assess the value of pre-treatment [¹⁸ F]FLT uptake in the prediction of treatment response and comparison to [¹⁸ F]FDG-PET.	Baseline [¹⁸ F]FLT SUV _{max} , MTV and TLG are strongly correlated to LRC and OS in univariate analysis. Moreover, TLG was an independent factor of LRC and SUV _{max} and MTV of OS in multivariate analyses. [¹⁸ F]FLT in general performed better than [¹⁸ F]FDG-PET.	Baseline [¹⁸ F]FLT uptake correlates well with clinical outcome and might be a prognostic factor in treatment of HNSCC.	[39]
48	HNSCC	RT or CHRT	Association between [¹⁸ F]FLT parameters and clinical outcome.	To monitor early treatment response using [¹⁸ F]FLT-PET in HNSCC and evaluating relationship between [¹⁸ F]FLT-PET parameters (SUV _{max9} ,	Significant decrease in [¹⁸ F]FLT-PET uptake was noticed between successive scans. Decrease in SUV _{max(9)} ≥ 45% during the first 2 weeks of treatment is associated	Favourable long-term outcome correlated significantly with greater decrease in [¹⁸ F]FLT-PET uptake in the second week of treatment.	[33]

46	HNSCC	CHRT	Relationship between tumour proliferation volume and clinical outcome.	To compare [¹⁸ F]FLT-PET segmentation methods (PV _{VIS} , PV _{RTL} , PV _{FLAB} and PV _{W&C}) for evaluating tumour proliferative volume and its relation to clinical outcome.	with better 3-year DFS 88% (95% CI: 75–100) versus 63% (95% CI: 41–85), p = 0.035. Baseline PV _{VIS} correlated best with PV _{FLAB} and GTV _{CT} (0.77, p < 0.001). A reduction in PV _{FLAB} above the median (7.39 cm ³) between the pre-treatment scan and the fourth week scan of CHRT was predictive of a better 4-year DFS (90 ± 9.5% versus 53 ± 17.6%, p = 0.04).	PV _{FLAB} PET segmentation method performed best in delineating tumour proliferative volume and determining clinical outcome. [32]
32	HNSCC	CHRT and surgery	The predictive potential of baseline [¹⁸ F]FLT for short-term clinical outcome.	To assess the correlation of baseline [¹⁸ F]FLT-PET metrics with loco-regional control and OS.	Baseline MTV, TLP and SUV _{peak} are associated with loco-regional control and OS (p < 0.05). Moreover, MTV and TLP was significantly lower in responders to therapy compared to non-responders.	Baseline [¹⁸ F]FLT-PET has potential to predict clinical outcome when MTV, TLP or SUV _{peak} are used. [40]
28	HNSCC	CHRT	Early response evaluation by [¹⁸ F]FLT-PET in HNSCC undergoing CHRT.	To evaluate the value of [¹⁸ F]FLT-PET in assessing locoregional clinical outcome of CHRT.	[¹⁸ F]FLT-PET uptake decreased gradually during RT than [¹⁸ F]FDG-PET uptake. The specificity and overall accuracy of [¹⁸ F]FLT-PET were significantly better than [¹⁸ F]FDG-PET both during and after treatment (p < 0.0001). Patient group with residual [¹⁸ F]FLT-PET uptake after treatment is associated with poor local tumour control when compared with no accumulation group (45% versus 97.5%, p < 0.0001).	[¹⁸ F]FLT-PET uptake has the potential to predict treatment outcome and identify patients at a risk of local failure. [34]
20	HNSCC	RT and CHRT	Value of [¹⁸ F]FLT-PET uptake in HNSCC patients.	To evaluate correlation between [¹⁸ F]FLT-PET uptake and Ki-67 index and if [¹⁸ F]FLT-PET uptake has prognostic value as determined by a correlation to patient survival.	No correlation was observed between [¹⁸ F]FLT-PET uptake and Ki-67 index, but significant inverse correlation was observed between [¹⁸ F]FLT-PET uptake (r = 0.53; p < 0.05) and patient survival.	High [¹⁸ F]FLT-PET uptake is associated with adverse prognosis. [35]
10	HNSCC	RT	Value of [¹⁸ F]FLT-PET/CT in oropharyngeal cancer patients.	To monitor early tumour response based on [¹⁸ F]FLT-PET/CT scans and to determine the feasibility of personalised adaptive radiotherapy to chemoradioresistant proliferative sub-volumes identified by [¹⁸ F]FLT-PET.	[¹⁸ F]FLT-PET defined SUV _{max} and SUV _{mean} decreased significantly just 1 week after start of treatment. However, GTV defined on CT (GTV _{CT}) decreased only after third week of treatment. Dose escalation to [¹⁸ F]FLT-PET defined active proliferative volumes (GTV _{80%} threshold) is technically feasible.	[¹⁸ F]FLT-PET defined tumour functional changes precede CT defined volumetric changes and therefore suitable for early tumour response assessment. [28]

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Table 1 (continued)

No. of patients	Tumour type	Treatment type	Clinical study	Purpose	Results	Conclusion(s)	Reference
50	NSCLC	TKI	Relationship between change in [¹⁸ F]FLT-PET uptake and clinical outcome in NSCLC.	To determine whether patients with [¹⁸ F]FLT-PET response on day 14 and 56 of erlotinib treatment had longer PFS and OS than patients without PET response.	Nine of 50 (18%) [¹⁸ F]FLT-evaluable patients had PMR at day 14. Four (7.8%) showed PR by day 56 CT; three of them had PMRs by day 14 [¹⁸ F]FLT-PET. Day 14 and day 56 PMRs by [¹⁸ F]FLT were associated with improved PFS. But [¹⁸ F]FLT-PET PMR was not associated with improved OS compared with [¹⁸ F]FLT-PET non-responders.	[¹⁸ F]FLT uptake 2 and 6 weeks after start of treatment show a correlation with PFS but not with OS. Furthermore, [¹⁸ F]FLT-PET scans identify more patients with PMR and more patients with progression than standard CT assessment.	[19]
40	NSCLC	Erlotinib (if progression CTx or RT)	Correlation between baseline [¹⁸ F]FLT uptake and clinical outcome.	Assessing the prognostic value of baseline [¹⁸ F]FLT-PET uptake in patients with metastatic NSCLC prior to systemic therapy with first-line erlotinib.	Low [¹⁸ F]FLT uptake at baseline (SUVmax < 3.0) was associated with longer survival (p = 0.027). However, [¹⁸ F]FLT-PET was not shown to be an independent prognostic factor in multivariate analysis (p = 0.077). SUVmax in baseline [¹⁸ F]FLT-PET shows an association with response to erlotinib treatment (p = 0.043). This was not translated into prolonged PFS in patients with low [¹⁸ F]FLT uptake.	[¹⁸ F]FLT-PET baseline uptake is significantly associated with longer survival and response to treatment in univariate analysis and, however, was not shown to be an independent prognostic factor in multivariate analysis in contrast to [¹⁸ F]FDG.	[14]
40	NSCLC	TKI	Clinical outcome and relationship with treatment induced changes in [¹⁸ F]FLT-PET parameters.	To evaluate the clinical benefit of first-line treatment with erlotinib using different quantitative parameters for [¹⁸ F]FLT-PET in advanced NSCLC patients.	Metabolic [¹⁸ F]FLT-PET response measured as proposed by the PERCIST guideline (1.0) 1 week after start of erlotinib showed a significantly longer PFS independent of the SUV used. This was not shown for response measurement after 6 weeks of treatment.	Early [¹⁸ F]FLT-PET measurements are correlated with PFS regardless of the method used for SUV calculation.	[15]
34	NSCLC	TKI	Treatment induced change in [¹⁸ F]FLT-parameters and correlation with clinical outcome.	To study the accuracy of [¹⁸ F]FLT-PET after 1 week of first-line erlotinib therapy for early prediction of non-progression after 6 weeks of therapy in patients with advanced NSCLC.	Four of six patients with an early [¹⁸ F]FLT response (≥30% reduction in SUVpeak), all having an absolute reduction of ≥0.4, were non-progressive after 6 weeks of treatment (p = 0.15). A significantly prolonged PFS was observed in patients with an early [¹⁸ F]FLT response (6.0 versus 1.6 months; p = 0.04.) Late [¹⁸ F]FLT response was not associated with improved PFS. Early and late [¹⁸ F]	Early [¹⁸ F]FLT response was associated with PFS but not with OS or non-progression after 6 weeks of treatment with erlotinib.	[17]

28	NSCLC	TKI	Predicting clinical outcome using [¹⁸ F]FLT imaging at baseline, after start of treatment and using treatment induced changes in [¹⁸ F]FLT-PET.	To assess the value of TLP determined by [¹⁸ F]FLT-PET for prediction of response and clinical outcome in patients with advanced NSCLC treated with erlotinib.	FLT responses were not associated with prolonged OS (OS, 16.0 versus 4.9 months, $p = 0.3$). Patients with a metabolic response ($>20\%$ reduction) measured by early TLP show a significantly better PFS than metabolically non-responders. Furthermore, patients with lower absolute early and late residual TLP levels had a significantly prolonged PFS. In contrast, absolute baseline TLG and TLP levels showed no significant association with PFS. Pre-treatment SUVmax did not differ between responders and non-responders on CT evaluation. At 7 d after the initiation of therapy, the percent changes in SUVmax were significantly different ($p < 0.001$). Change in [¹⁸ F]FLT uptake has high positive and negative predictive values. TTP is significantly longer in [¹⁸ F]FLT-PET responders than non-responders ($p = 0.004$). The median OS for patients with and without [¹⁸ F]FLT-PET response was not significantly different ($p = 0.26$).	Reduction in TLP of $>20\%$ and absolute residual TLP levels under erlotinib treatment emerged as predictive factors for PFS in patients with NSCLC. [18]
28	NSCLC	TKI	Change in [¹⁸ F]FLT-PET after treatment and relation with clinical response.	To evaluate the usefulness of [¹⁸ F]FLT-PET for predicting response and clinical outcome of gefitinib therapy in patients with adenocarcinoma of the lung.	Pre-treatment SUVmax did not differ between responders and non-responders on CT evaluation. At 7 d after the initiation of therapy, the percent changes in SUVmax were significantly different ($p < 0.001$). Change in [¹⁸ F]FLT uptake has high positive and negative predictive values. TTP is significantly longer in [¹⁸ F]FLT-PET responders than non-responders ($p = 0.004$). The median OS for patients with and without [¹⁸ F]FLT-PET response was not significantly different ($p = 0.26$).	[¹⁸ F]FLT-PET is correlated to TTP and can predict response to TKI early after start of treatment in non-smokers with NSCLC. The change in tumour SUVmax seems to have a promising predictive value. [16]
20	NSCLC	RT	Change in [¹⁸ F]FLT-PET/CT during carbon ion radiotherapy.	To evaluate the clinical value of [¹⁸ F]FLT-PET/CT in lung cancer patients receiving carbon ion radiotherapy.	Tumour [¹⁸ F]FLT-PET uptake decreased significantly after treatment ($p < 0.001$). However, radiation pneumonitis hampered precise [¹⁸ F]FLT-PET uptake evaluation. Patients who developed recurrence or who died of lung cancer during follow-up had high pre-treatment [¹⁸ F]FLT-PET uptake than that of patients who did not ($p = 0.008$, $p = 0.007$). Also in patients with SUVmax <3.7 showed significantly better prognosis ($p = 0.003$ for PFS and $p = 0.002$ for DFS).	Pre-treatment [¹⁸ F]FLT-PET SUVmax carries prognostic value and may contribute to decision making on the treatment approach. [30]

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Table 1 (continued)

No. of patients	Tumour type	Treatment type	Clinical study	Purpose	Results	Conclusion(s)	Reference
14	NSCLC	TKI	Relationship between [¹⁸ F]FLT-PET uptake and clinical outcome.	To study the diagnostic efficacy of [¹⁸ F]-FLT for response evaluation following 3 weeks of treatment with EGFR-TKI in NSCLC patients.	[¹⁸ F]FLT SULpeak values show no significant correlation with PFS (p = 0.2) and OS (p = 0.07). Using a ROC curve responders were defined as a decrease of ≥22% in [¹⁸ F]FLT SULpeak and a decrease of ≥0.7 in absolute values. This gave a sensitivity and specificity of 100%.	No correlation was found between [¹⁸ F]FLT SULpeak and OS and PFS in patients treated with EGFR-TKI for 3 weeks.	[20]
11	NSCLC	CTx	Value of [¹⁸ F]FLT-PET in NSCLC.	To evaluate the effect of pemetrexed induced TS inhibition on [¹⁸ F]FLT-PET scan 4 h after pemetrexed administration in stage IV NSCLC patients.	All patients showed decreased deoxyuridine levels after pemetrexed administration indicating pemetrexed induced TS inhibition. However, no significant correlation was observed between [¹⁸ F]FLT-PET uptake and clinical outcome. Also, baseline was not predictive for tumour response (p = 0.86).	A non-systematic change in [¹⁸ F] FLT-PET uptake was observed 4 h after pemetrexed administration. However, the association between [¹⁸ F]FLT-PET uptake and TTP, OS or tumour response was not significant.	[21]
7	NSCLC	RT	Change in [¹⁸ F]FLT-PET uptake due to RT alone.	To evaluate whether [¹⁸ F]FLT-PET changes occur early in response to radiotherapy without concurrent chemotherapy.	Primary tumours SUVmean reproducibility (SD 8.9%) is better than SUVmax reproducibility (SD 12.6%). Primary tumour SUVmean decreased significantly by 25% after 5–11 radiotherapy fractions in the absence of significant volumetric change (p = 0.0001). Locoregional tumour control was found to be associated with primary tumour SUVmax at radiotherapy (HR: 2.3 CI: 1.06–5.0, p = 0.03) but not with SUVmax at baseline (HR: 1.46, CI: 0.97–2.18, p = 0.068).	[¹⁸ F]FLT-PET is a valuable clinical tool to report early on radiation response and to intensify treatment for patients with increased [¹⁸ F] FLT-PET uptake to further improve locoregional tumour control.	[31]
62	DLBCL	CTx	Relationship between baseline [¹⁸ F]FLT-PET and treatment response and clinical outcome.	To correlate the initial [¹⁸ F]FLT uptake with the clinical outcome of patients with DLBCL treated with standard R-CHOP.	Baseline SUVmean was significantly lower in CR groups (SUVmean: 7.1; range: 1.0–18.2) than non-CR groups (partial response and progressive disease, SUVmean 9.4, range: 1.2–20.4, p = 0.049). Also, significant positive correlation was observed between [¹⁸ F]FLT-PET SUVmean and IPI risk groups (p < 0.001). No correlation between baseline [¹⁸ F]FLT uptake and OS.	Baseline [¹⁸ F]FLT uptake is correlated with treatment response and high [¹⁸ F]FLT uptake is a negative predictor of response to R-CHOP treatment in DLBCL.	[11]

61	NHL	CTx	Relationship between change in [¹⁸ F]FLT parameters and clinical outcome in NHL.	To evaluate the prognostic value of early [¹⁸ F]FLT-PET in patients with NHL.	Patients who were defined as [¹⁸ F]FLT-PET positive (SUVmax > 1.86) after one cycle and at the end of chemotherapy or [¹⁸ F]FLT-PET positive after one cycle and negative at the end of treatment had significant worse 5-year PFS and OS rates (p < 0.001) then early PET-negative patients. Multivariable analyses shows that the prognostic value of interim [¹⁸ F]FLT-PET positivity by remained significant after adjustment with other prognostic factors (PFS and OS, p = 0.009 and p = 0.014, respectively).	[¹⁸ F]FLT-PET positivity after one cycle of chemotherapy has a significant correlation with worse PFS and OS compared to PET- ¹⁸ F]FLT negative patients.	[13]
54	DLBCL	CTx	Treatment induced change in [¹⁸ F]FLT uptake and correlation with treatment response.	To prospectively assess if [¹⁸ F]FLT uptake and the decrement of [¹⁸ F]FLT uptake after 1 week of immunochemotherapy are suitable to predict response and clinical outcome in patients with DLBCL.	SUVmean and SUVmax decrease 1 week after chemotherapy was significantly higher in patients achieving complete response. Martingale-residual and Cox proportional hazard analyses showed a significant monotonous decrease of mortality risk with increasing change in SUV. The corresponding estimated hazard ratios per point increment of SUVmean and SUVmax were 0.65 (p = 0.001) and 0.60 (p = 0.002), respectively.	Change in [¹⁸ F]FLT-PET 1 week after the start of R-CHOP chemotherapy is correlated with clinical response and survival.	[12]
22	NHL	CTx	Correlation of baseline [¹⁸ F]FLT-PET and treatment induced change with treatment response.	To evaluate [¹⁸ F]FLT-PET for early monitoring response of high-grade NHL to treatment with chemotherapy with or without rituximab (R-CHOP/CHOP).	There was no statistically significant difference between initial [¹⁸ F]FLT-uptake in patients with PR or CR, as indicated by the CT scan. All patients responding to chemotherapy showed significant reduction of [¹⁸ F]FLT uptake. There was a significant difference in [¹⁸ F]FLT retention between patients reaching PR versus CR at the end of therapy.	[¹⁸ F]FLT-PET was significantly correlated to PR and CR and seems to be promising for early evaluation of therapy in lymphoma.	[10]
8	AML	CTx	Correlation between [¹⁸ F]FLT parameters and treatment response.	To investigate the use of [¹⁸ F]FLT-PET for assessment of early treatment response in patients with AML.	[¹⁸ F]FLT uptake in bone marrow was significantly lower in patients with CR compared to those with RD after 2 weeks of chemotherapy (p < 0.001). These results were independent of time of assessment.	[¹⁸ F]FLT-PET may serve as an early biomarker of response to treatment in AML.	[41]

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Table 1 (continued)

No. of patients	Tumour type	Treatment type	Clinical study	Purpose	Results	Conclusion(s)	Reference
18	mCRC	CTx	Early prediction of response and clinical outcome using change in [¹⁸ F]FLT parameters after treatment.	To evaluate [¹⁸ F]FLT-PET for early prediction anatomic response and survival outcomes in patients with mCRC receiving FOLFOX.	[¹⁸ F]FLT-PET SUVmax was increased compared with baseline values both in responders and non-responders on day 2 after start of treatment (p = 0.043 and p < 0.001, respectively). A SUVmax increase of ≤45.8% on day 2 (low [¹⁸ F]FLT flare) optimally differentiated between responders and non-responders. Patients with low [¹⁸ F]FLT flare on day 2 tended to have longer survivals than patients with high flare (2-year overall survival rate, 77.8% versus 44.4%, p = 0.051). Responders showed a decreased SUVmax compared to baseline on day 5 (p = 0.043). No significant differences were found in PFS or OS.	The height of the [¹⁸ F]FLT flare observed during 5-FU infusion was correlated with treatment response in patients with mCRC. The degree of [¹⁸ F]FLT flare was also associated with poor clinical outcome of patients who receive continues infusion of 5-FU–based chemotherapy.	[27]
14	Rectal cancer	CHRT	[¹⁸ F]FLT-PET as a predictor of outcome in rectal cancer patients.	To evaluate whether baseline and early during treatment [¹⁸ F]FLT-PET uptake of tumour is a predictor of outcome in locally advanced rectal cancer patients.	[¹⁸ F]FLT-PET uptake decreased significantly after therapy from baseline. Low [¹⁸ F]FLT-PET uptake during treatment and change in [¹⁸ F]FLT-PET uptake ≥60% were predictors of DFS (p < 0.05). However, pre-treatment [¹⁸ F]FLT-PET uptake did not correlate with DFS. Also, no significant correlation was found between ΔSUV and histopathological tumour regression.	Early [¹⁸ F]FLT-PET uptake (SUVmax < 2.2) during treatment predicts DFS in locally advanced rectal cancer patients.	[37]
45	Gastric cancer	CTx	Correlation of [¹⁸ F]FLT parameters at baseline, during treatment and change in [¹⁸ F]FLT parameters with clinical outcome and response.	To assess whether [¹⁸ F]FLT-PET can improve the predictive potential of molecular imaging for assessing response to neoadjuvant therapy in gastric cancer compared with [¹⁸ F]FDG-PET.	No significant correlation between clinical response and baseline SUV, absolute SUV after 2 weeks of treatment or change in SUV after treatment was found. Univariate Cox regression analysis revealed significant prognostic impact for survival only for [¹⁸ F]FLT SUVmean day 14 (p = 0.048). Multivariate Cox regression analysis [¹⁸ F]FLT SUVmean day	[¹⁸ F]FLT uptake 2 weeks after initiation of therapy was shown to be the only imaging parameter with significant prognostic impact. Neither [¹⁸ F]FLT-PET nor [¹⁸ F]FDG-PET were correlated with histopathological or clinical response.	[42]

20	Pancreatic cancer	CTx	Treatment induced change in [¹⁸ F]FLT uptake and correlation with clinical outcome and response to treatment.	To investigate early response assessment using [¹⁸ F]FLT PET/CT in pancreatic cancer patients.	14 as the only significant prognostic factors (p = 0.002). A significant correlation was found between [¹⁸ F]FLT-PET response and response assessment on RECIST after three months of treatment (p = 0.04). An increase in SUVmax of 12% optimally differentiated non-responders and, however, was not predictive for PFS and OS (p > 0.5).	[¹⁸ F]FLT-PET could be used to assess response to chemotherapy in pancreatic cancer. No correlation was found with clinical outcome and, however, larger studies are needed since this study was not powered to evaluate PFS and OS.	[43]
34	Oesophageal cancer	RT and CHRT	Correlation of baseline [¹⁸ F]FLT uptake and change after treatment with clinical outcome.	To evaluate the prognostic value of treatment response assessed with [¹⁸ F]FLT-PET in oesophageal cancer and compare it with [¹⁸ F]FDG-PET.	A decrease in [¹⁸ F]FLT-PET SUVmax of >60% 4 weeks after start of treatment showed the strongest correlation with better 2-year PFS and LRC (p = 0.025 and 0.046, respectively). [¹⁸ F]FLT uptake had a stronger correlation with clinical-outcome in patients receiving CHRT compared to RT alone. No association with OS was found for any of the parameters.	Follow-up using interim [¹⁸ F]FLT-PET could be used for prediction of PFS and LRC in oesophageal cancer and seems to be superior to [¹⁸ F]FDG-PET.	[36]
9	Oesophageal cancer	CTx	Early tumour response evaluation by [¹⁸ F]FLT-PET in resectable oesophageal cancer patients.	To determine the feasibility of [¹⁸ F]FLT-PET in predicting early tumour response after induction chemotherapy followed by concurrent CHRT in resectable oesophageal cancer patients.	[¹⁸ F]FLT-PET SUVmax decreased significantly after the induction chemotherapy (median 7.7–2.8, p = 0.0012) in responders while little decrease was observed in the non-responder (median 4.9–4.4). Eventually, the non-responder was found with liver metastases during surgery.	Change in primary tumour SUVmax might be a good parameter for the prediction of concurrent CHRT response in oesophageal cancer patients. Most importantly, [¹⁸ F]FLT-PET may recommend earlier alterations of treatment strategies in non-responders.	[26]
30	Glioma	CTx and bevacizumab	Early prediction of clinical outcome using treatment induced change in [¹⁸ F]FLT uptake.	To assess the value of [¹⁸ F]FLT for early outcome predictions in patients treated for recurrent glioma.	Change in [¹⁸ F]FLT uptake 2 and 6 weeks after start of treatment is predictive of PFS and OS in univariate and multivariate analyses. Survival was 3.3 times as long in responders (>25% decrease). Change 6 weeks after start of treatment showed the strongest correlation (p = 0.001).	Change in [¹⁸ F]FLT-PET is correlated to PFS and OS, and, therefore could be used as an predictive tool to assess clinical outcome in recurrent glioma.	[25]
19	Glioma	CTx and bevacizumab	Change in [¹⁸ F]FLT uptake and association with clinical outcome.	To determine if early and/or late [¹⁸ F]FLT-PET can predict outcome and treatment response in patients treated for recurrent glioma.	Both early and late change in [¹⁸ F]FLT uptake after the start of treatment was predictive for overall survival. Patients showing a 25% reduction in [¹⁸ F]FLT uptake tended to have prolonged OS and PFS. [¹⁸ F]FLT at any time point did not predict clinical outcome.	Reduction in [¹⁸ F]FLT-PET uptake 1–2 as well as 6 weeks after start of treatment correlated well with clinical outcome.	[24]

(continued on next page)

Table 1 (continued)

No. of patients	Tumour type	Treatment type	Clinical study	Purpose	Results	Conclusion(s)	Reference
13	Mucosal melanoma	RT	Prediction of clinical outcome using baseline [¹⁸ F]FLT-PET and change after during carbon ion radiotherapy.	To determine the predictive and prognostic value of [¹⁸ F]FLT-PET for response to treatment in patients with mucosal malignant melanoma.	Pre-treatment SUVmax ≥ 4.3 and ≥ 5.0 are prognostic factors for better OS and metastasis-free survival, respectively. Change in [¹⁸ F]FLT uptake of $\geq 35\%$ 4 weeks after start of treatment only showed a correlation with LRC. Post-treatment SUVmax did not correlate with clinical outcome.	[¹⁸ F]FLT-PET might be useful to predict clinical outcome in mucosal melanoma patients treated with carbon ion radiotherapy.	[44]
11	Germ cell Tumours	CTx	Early response monitoring using [¹⁸ F]FLT uptake and prediction of viable residual tumour in patients with metastatic GCT.	To assess the diagnostic efficacy of [¹⁸ F]FLT PET compared to [¹⁸ F]FDG-PET for early response monitoring and prediction of residual viable tumour after chemotherapy of metastatic GCT.	In responders and non-responders, the mean SUV of [¹⁸ F]FLT decreased by 58% and 48%, respectively, ($p = 0.5$). At the end of therapy, these were decreased to 68% and 65%, respectively ($p = 0.8$). The sensitivity, specificity, positive and negative predictive value for detection of viable tumour after the first cycle of chemotherapy were 60%, 80%, 75%, and 67%, respectively. After the end of chemotherapy, these were 0%, 100%, 0%, and 50%.	[¹⁸ F]FLT cannot improve prediction of viable residual tumour in patients with metastatic GCT compared to [¹⁸ F]FDG, because of the low negative predictive value. Prediction of response cannot be replaced by early [¹⁸ F]FLT and [¹⁸ F]FDG response evaluation.	[45]

Abbreviations: [¹⁸F]FLT = [¹⁸F]-fluorothymidine; FDG = [¹⁸F]-fluorodeoxyglucose; PET = positron emission tomography; HNSCC = head and neck squamous cell carcinomas; NSCLC = non-small-cell lung carcinoma; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin's lymphoma; mCRC = metastasised colorectal cancer; GCT = germ cell tumour; AML = acute myeloid leukaemia; CHRT = chemoradiotherapy; RT = radiotherapy; CTx = chemotherapy; C/E = cisplatin/etoposide; C/P = carboplatin/paclitaxel; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CHOP = CHOP with rituximab; FOLFOX = folinic acid, fluorouracil and oxaliplatin; 5-FU = fluorouracil; TS = thymidylate synthase; PV_{VIS} = proliferative tumour volume delineated visually; PV_{RTL} = proliferative tumour volume delineated using a background-subtracted relative threshold level; PV_{FLAB} = proliferative tumour volume delineated using a fuzzy locally adaptive Bayesian algorithm; PV_{W&C} = proliferative tumour volume delineated using a gradient-based method using the watershed transform algorithm and hierarchical clustering analysis; GTV_{CT} = gross tumour volumes visually delineated on computed tomographic images; GTV_{50%} = gross tumour volumes delineated using a 50% isocontour of the maximum signal intensity; GTV_{SBR} = gross tumour volumes delineated using signal-to-background ratio; SUV = standardised uptake value; SUVmax = maximum standardised uptake value; SUVmean = mean standardised uptake value; SUVmax(9) = mean maximum standardised uptake values for the hottest voxel in the tumour and its eight surrounding voxels in one transversal slice; TLG = total lesion glycolysis; TLP = tumour lesion proliferation; SULpeak = SUV corrected for lean body mass; MTV = metabolic tumour volume DFS = disease-free survival; PFS = progression-free survival; TTP = time to progression; CR = complete remission; PR = partial response; PMR = partial metabolic response; OS = overall survival; HR = hazard ratio; CI = confidence interval; LRC = locoregional tumour control; SD = standard deviation; CA = cancer antigen; IPI = International Prognostic Index; ROC = receiver operating characteristic.

who also studied prognostic value of [^{18}F]FLT in 61 NHL patients.

Similar studies were performed in non-small-cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors (TKIs) (Fig. 2). Baseline [^{18}F]FLT-PET SUVmax <3.0 proved to be a prognostic indicator (hazard ratio [HR] 2.2, $p = 0.027$), correlating significantly with response to treatment and prolonged survival in patients with metastatic NSCLC treated with erlotinib ($n = 40$) [14]. Kahraman et al. [15] evaluated the clinical benefit of first-line treatment with erlotinib using [^{18}F]FLT-PET in 40 patients with advanced NSCLC. [^{18}F]FLT-PET response was measured as proposed by the PERCIST (1.0) guidelines. [^{18}F]FLT-PET scans 1 week after start of erlotinib treatment predicted progression-free survival (PFS) showing potential for response prediction. These results are supported by data of three other studies showing that change in [^{18}F]FLT-PET, 1 week after start of erlotinib therapy correlated with PFS (HR: 0.30, $p = 0.04$) [16–18]. This correlation was also found when response evaluation is performed after 2 weeks, but data obtained 3 or 6 weeks after start of TKI treatment were ambiguous, indicating the importance of an adequate time interval for scanning [17,19,20].

Regardless of timing, change in [^{18}F]FLT uptake showed no correlation with overall survival (OS) ($p > 0.07$) in NSCLC patients, this in contrast to [^{18}F]FLT response evaluation in NHL [16,17,19–21]. This discrepancy might be due to differences in effect size of chemotherapy and TKI treatment; hence, larger studies might be needed to demonstrate correlation between treatment with TKI and OS. In many of the studies on

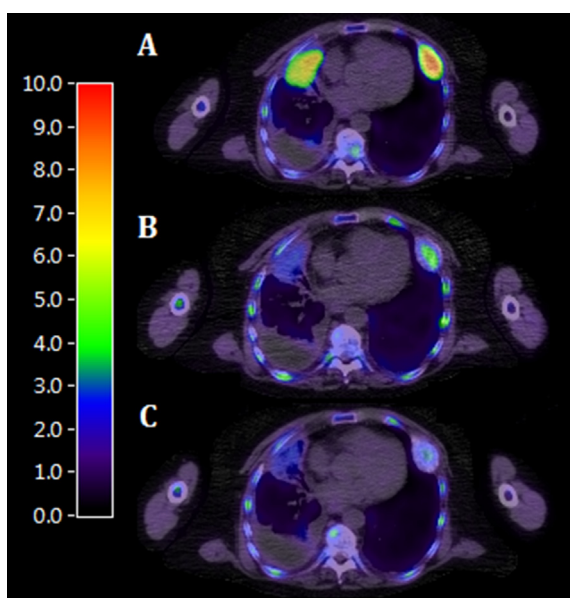


Fig. 2. An [^{18}F]fluorothymidine positron emission tomography/computed tomography scan of a non-small-cell lung cancer patient before (A), after 7 d (B) and 26 d (C) after start of tyrosine kinase inhibitor treatment.

NSCLC, performance of [^{18}F]FLT-PET was also compared to [^{18}F]FDG-PET, which often yielded better correlations with PFS and OS [14]. Therefore, the additional value of [^{18}F]FLT-PET for evaluation of treatment response in NSCLC might be limited.

Subsequently, several other studies reported on the utility of [^{18}F]FLT-PET in prediction of early tumour response for other tumour types. Contractor et al. [22] performed dynamic scans at baseline and 2 weeks after the first or second cycle of docetaxel in 20 breast cancer patients. The decrease in [^{18}F]FLT-PET uptake observed at 60 min was significantly larger for responders than non-responders (40.2% versus 10.5%) and authors concluded that change in [^{18}F]FLT-PET early after initiating docetaxel is associated with target lesion response mid-therapy. Moreover, another study showed that change in [^{18}F]FLT-PET uptake after one cycle chemotherapy could predict tumour response in breast cancer patients ($n = 14$) [23]. The decline of [^{18}F]FLT-PET tumour uptake 1 week after start of chemotherapy also showed a correlation with clinical response ($n = 13$) [2].

[^{18}F]FLT-PET has also been studied in patients with recurrent high-grade glioma treated with bevacizumab and irinotecan [24]. [^{18}F]FLT-PET scans acquired at 2 weeks after start of treatment found that SUVmean significantly predicted overall survival ($p = 0.006$). Similar results were reported by others, confirming the value of [^{18}F]FLT-PET tumour uptake in predicting tumour response to chemotherapy [25].

Furthermore, a study was performed to prospectively evaluate [^{18}F]FLT-PET as imaging biomarker to determine the early impact of induction chemotherapy before concurrent chemoradiotherapy (CHRT) in resectable oesophageal cancer patients ($n = 9$) [26]. Eight patients with complete or partial response showed a decrease in [^{18}F]FLT-PET uptake values after induction chemotherapy (median: 57.1%), while the non-responder showed little change in [^{18}F]FLT-PET uptake (median: 10.2%). This study suggests that early decrease in [^{18}F]FLT-PET uptake after induction chemotherapy might be useful for predicting treatment response in these patients.

In all former studies, a decrease of [^{18}F]FLT uptake after start of therapy was correlated to better response. This decrease is interpreted as a decrease in proliferation rate and demand of thymidine. However, treatment with drugs interfering with endogenous thymidine synthesis (e.g. 5-fluorouracil) may result in a flare of [^{18}F]FLT uptake due to an increase in TK1 activity. In 18 patients with metastasised colorectal cancer, Hong et al. [27] observed an inverse correlation between the height of the flare and response to treatment. Patients with low flares also tended to have longer survival. This suggests that the degree of [^{18}F]FLT flare might be useful to predict the outcome of patients who undergo 5-FU-based chemotherapy; however, this has to be further explored.

3.3. Radiotherapy

Serial [¹⁸F]FLT-PET scans have been performed in patients with oropharyngeal cancer by Troost et al. [28]. Ten patients underwent three consecutive [¹⁸F]FLT-PET scans, at baseline and 2 and 4 weeks after start of radiotherapy to assess early tumour response, tumour heterogeneity and identifying tumour sub-volumes with active proliferation. SUV_{max} and SUV_{mean} decreased significantly as early as 1 week after start of treatment and continued to decrease up to the fourth week of treatment (SUV_{mean}: 4.7 ± 1.6 , 2.0 ± 0.9 and 1.3 ± 0.2 ; $p < 0.001$). The decrease in [¹⁸F]FLT uptake was more than two-fold in the initial phase of treatment and a further two-fold decrease in the fourth week after start of treatment. These results suggest that [¹⁸F]FLT-PET can assess treatment response much earlier than [¹⁸F]FDG-PET. Likewise, another group also showed a significant decrease in [¹⁸F]FLT-PET uptake after 10 Gy of radiotherapy in head and neck squamous cell carcinoma (HNSCC) patients [29]. Troost et al. [28] observed a significant decrease in gross tumour volume delineated on CT (GTV_{CT}) only at the end of treatment (GTV_{CT} in cubic centimetres: 12.7 ± 9.5 , 11.1 ± 8.8 and 5.0 ± 4.7). Hence, [¹⁸F]FLT-PET uptake precedes CT tumour response and is therefore valuable for early treatment response. Furthermore, it appears that residual [¹⁸F]FLT-PET tumour sub-volumes within the tumour at 2 weeks after start of treatment should receive higher radiation doses to improve locoregional tumour control (LRC) and consequently OS. In this regard, a well-demarcated proliferative area at [¹⁸F]FLT-PET 2 weeks after start of RT seems to be appropriate and can be treated with spatially conformed doses by precisely targeting tumour proliferation.

The clinical value of [¹⁸F]FLT-PET/CT imaging before and 3 months after carbon ion radiotherapy was evaluated by Saga et al. [30] in NSCLC patients ($n = 20$). No correlation between SUV_{max} after treatment or treatment induced change and local recurrence, development of metastasis or survival was demonstrated. Yet, they showed that all NSCLC patients who developed recurrence or who died of lung cancer during follow-up had higher pre-treatment [¹⁸F]FLT-PET uptake compared to patients who did not ($p = 0.008$, $p = 0.007$). These results suggest the possibility of using [¹⁸F]FLT-PET as tool for patient stratification and risk assessment; however, this requires validation in larger cohorts. Trigonis et al. [31] showed that SUV_{mean} reproducibility (standard deviation [SD]: 8.9%) in primary tumours was better than SUV_{max} reproducibility (SD: 12.6%) in NSCLC patients ($n = 16$). They also showed that primary tumour SUV_{mean} decreased significantly by 25% ($p = 0.001$) after 5–11 fractions of RT in the absence of tumour morphological change. However, conforming the previous results, this decrease was correlated neither to OS nor to LRC rates.

3.4. Chemoradiotherapy

Changes in an imaging biomarker to evaluate pathological and physiological response can play a vital role in recognising an appropriate therapeutic agent. For example, the association between elevated tumour proliferation and increased incidence of tumour growth and resistance to treatment provides an underlying rationale for enhanced radiation dose delivery to the proliferative volume of the tumour [17]. Therefore, accurate delineation of the proliferative tumour volume (PV) is pivotal for delivering radiotherapy based on the repopulation response and subsequently clinical outcome.

To evaluate proliferative volume of the tumour and its relation to clinical outcome in HNSCC, Arens et al. [32] compared different [¹⁸F]FLT-PET segmentation methods: 1) PV_{VIS}: visual delineation, 2) PV_{RTL}: relative threshold level, 3) PV_{FLAB}: fuzzy locally adaptive Bayesian, and 4) PV_{W&C}: watershed transform and hierarchical clustering. Forty-six patients treated with CHRT underwent [¹⁸F]FLT-PET/CT at baseline and in the second and fourth weeks of treatment. A reduction in PV_{FLAB} above the median (7.39 cm^3) between the pre-treatment scan and the fourth week scan was predictive of a better 4-year disease-free survival (DFS) ($90 \pm 9.5\%$ versus $53 \pm 17.6\%$, $p = 0.04$). The PV_{FLAB} obtained at 2 and 4 weeks after start of treatment showed no correlation with LRC and OS.

In another study, Hoeben et al. [33] evaluated operator-dependent (PET-segmented GTV using visual delineation [GTV_{VIS}] and mean SUV_{max} uptake values for the hottest voxel in the tumour and its eight surrounding voxels in one transverse plane [SUV_{max(9)}]) and operator-independent (50% isocontour of the SUV_{max} [GTV_{50%}]) and signal-to-background ratio [GTV_{SBR}]) segmentation methods to delineate tumour volumes on the sequential [¹⁸F]FLT-PET/CT scans in stage II–IV HNSCC patients ($n = 48$). A decrease in SUV_{max(9)} $\geq 45\%$ and a GTV_{VIS} decrease \geq median during the first 2 weeks of treatment is associated with better 3-year DFS 88% (95% confidence interval [CI]: 75–100) versus 63% (95% CI: 41–85). Operator-independent segmentation methods could not accurately define tumour areas during treatment due to fading signal-to-background ratios. Overall, an early decrease in [¹⁸F]FLT-PET uptake (second week) during treatment is associated with favourable treatment outcome.

Recently, Kishino et al. [34] assessed early treatment response evaluation by [¹⁸F]FLT-PET in HNSCC patients. In this study, all patients ($n = 28$) underwent [¹⁸F]FLT and [¹⁸F]FDG-PET scans at baseline, 4 weeks after the start of CHRT and 5 weeks after the completion of treatment. The specificity and accuracy of [¹⁸F]FLT-PET scans were significantly higher than [¹⁸F]FDG-PET scans both during and after radiotherapy. Again potential was demonstrated in HNSCC for predicting outcome

to treatment with significant differences in 3-year LRC between no-accumulation and residual accumulation groups for post-treatment [^{18}F]FLT-PET scans (HR: 25.6, $p < 0.001$). [^{18}F]FLT and [^{18}F]FDG scans were also performed to assess radiotherapy or CHRT treatment response in HNSCC patients ($n = 20$) by Linecker et al. [35]. Although no correlation was observed between Ki-67-positive cells and [^{18}F]FLT-PET uptake, a significant correlation was found between [^{18}F]FLT-PET uptake and OS ($r = 0.53$, $p < 0.05$).

These results combined suggest that [^{18}F]FLT-PET is a promising tool for early response assessment of radiotherapy in HNSCC and may differentiate lesions from radiotherapy-induced inflammation more effectively than [^{18}F]FDG-PET. Comparable results are seen in oesophageal cancer patients ($n = 34$) where PFS and LRC are significantly correlated with change in [^{18}F]FLT uptake 4 weeks after start of RT or CHRT [36]. However, both tumour types require further studies to elucidate the connection of [^{18}F]FLT-PET uptake with survival in larger patient population.

The value of [^{18}F]FLT-PET imaging for monitoring tumour response to pre-operative CHRT in patients with locally advanced rectal cancer ($n = 14$) was also evaluated [37]. Significant reduction in tumour [^{18}F]FLT-PET uptake was observed 2 weeks after start of neoadjuvant CHRT ($p < 0.0001$). Authors demonstrated that low [^{18}F]FLT-PET uptake during treatment (SUVmax < 2.2) and high percentage change in [^{18}F]FLT-PET uptake ($\geq 60\%$) significantly predicted DFS ($p < 0.005$) for all uptake metrics, respectively. However, their results did not correlate with histopathological response. Similar results were reported in another study ($n = 10$) where [^{18}F]FLT-PET uptake showed a significant decrease between baseline and 2 weeks after start of treatment (4.2 ± 1.0 to 2.9 ± 0.6 , $-28.6 \pm 10.7\%$, $p = 0.005$), with an additional decrease at the pre-operative PET scan (1.09 ± 0.4 , $-54.7 \pm 7.6\%$, $p = 0.005$) [38]. Yet, change in [^{18}F]FLT uptake also did not correlate with pathological response. It is thought that the lack of the correlation is related to inadequate tracer delivery due to poor blood supply secondary to radiotherapy. Next, due to lack of statistical power in both studies, caution is necessary when interpreting these results. Additional studies are required to establish the value of [^{18}F]FLT-PET imaging in rectal cancer.

3.5. Limitations

The studies described above have several limitations. Firstly, all studies are single-centre observational studies with small sample sizes. Due to these small sample sizes, studies might be underpowered to confirm correlations with clinical outcome and treatment response and correct interpretation of results could be impaired. Secondly, many studies defined thresholds retrospectively.

Therefore, to validate these thresholds and to further confirm the impact of [^{18}F]FLT as imaging biomarker of treatment response, interventional studies with larger patient populations are needed.

Finally, imaging procedures have to be standardised to obtain comparable results within different studies. Up to now, several imaging protocols are used with differences in uptake time, time per bed position and acquisition methods which could influence quantitative analyses and decrease comparability of results.

4. Conclusion

Overall, [^{18}F]FLT-PET seems to be a good predictor of early response to systemic-, radio- and concurrent chemoradiotherapy. PFS and DFS show good correlations with [^{18}F]FLT uptake; however, the correlation with overall survival is less consistent. Moreover, it is of great importance to perform the response assessment at an adequate time interval. If change in [^{18}F]FLT response is assessed too soon or too late after start of treatment, the discriminative power of [^{18}F]FLT-PET might be compromised. Furthermore, [^{18}F]FLT-PET might be developed into a tool for guiding individualisation of treatment strategies as it is able to detect active proliferative tumour sub-volumes and could provide additional information on chemoradioresistant areas. However, up to now, mostly observational studies have been performed and larger interventional studies assessing the clinical impact of [^{18}F]FLT as imaging biomarker are required.

Conflict of interest statement

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under grant agreement number 115151, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies' in-kind contribution. There was, however, no financial or in-kind contribution from EFPIA companies to the research specifically described in this paper.

Disclosure

The publication content is solely the responsibility of the authors and does not necessarily reflect the view of Fonds Cancer.

Acknowledgements

The research leading to these results has received support from the Innovative Medicines Initiative Joint

Undertaking (www.imi.europa.eu) under grant agreement no. 115151, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution. This presentation reflects the authors' view and neither the IMI JU nor the European Union and EFPIA are liable for any use that may be made of the information contained herein. This research was also supported by the Fonds Cancer from Belgium for the support of the fellowship of Vikram rao Bollineni.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2015.11.018>.

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