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REVIEW ARTICLE

# The role of dual and multiple time point imaging of FDG uptake in both normal and disease states

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**Abstract** Dual time point imaging (DTPI) and delayed time point imaging have been used for the differentiation of inflammatory and malignant processes and found to enhance the specificity of FDG PET imaging for diagnostic and prognostic purposes. It has been shown that the degree of FDG uptake at the second acquisition time point after the baseline scan increases in malignant cells; in inflammatory or infectious disorders, on the other hand, FDG uptake decreases or remains unchanged at the second time point. Many groups have investigated the application of DTPI and its potential and limitations have been discussed in detail with reference to a wide variety of malignant diseases, including those of the lung. The aim of this review is to describe the role of DTPI to assess both normal and disease states.

**Keywords** FDG PET/CT · Dual time point imaging · Inflammation · Malignancy · Lung cancer

## Introduction

In the last two decades $^{18}$F-FDG PET/CT, a powerful modality able to characterize cancer biology, has made major contributions to the practice of oncology, specifically in disease staging and restaging and in the monitoring of treatment in many malignancies [1]. The accumulation of FDG in cells, following its phosphorylation to FDG-6-phosphate by hexokinase, is facilitated by the glycolytic pathway (Fig. 1). This biological pathway allows the characterization of tumor biology and also makes it possible to differentiate malignant cells from normal and inflammatory cells. However, it has now been demonstrated that both inflammatory and infectious disorders have increased glycolytic activity and therefore can mimic malignancy in many settings [2]. Dual time point imaging (DTPI) and delayed time point imaging have been used as two means of differentiating between these two different processes and have thus enhanced the specificity of FDG PET imaging for diagnostic purposes (Fig. 2) [3–14].

Through in vitro and in vivo imaging experiments, it has been shown that the degree of FDG uptake at the second acquisition time point after the baseline scan increases in malignant cells; in inflammatory or infectious disorders, on the other hand, FDG uptake decreases or remains unchanged at the second time point [2]. The extent of FDG uptake and its clearance depend on the time delay between injection of FDG and the acquisition of images of the disease sites. The cells of highly glycolytic tissues continuously trap FDG in the form of FDG-6-phosphate, which may remain intact or be dephosphorylated by the enzyme glucose-6-phosphatase inside the cell. It has been speculated that the level of glucose-6-phosphatase is one of the factors that, through DTPI, make it possible to differentiate malignant from benign lesions [15–17]. Cancer cells likely contain low levels of glucose-6-phosphatase for dephosphorylation of FDG-6-phosphate and this could explain the continuous accumulation of FDG-6-phosphate in malignant cells,

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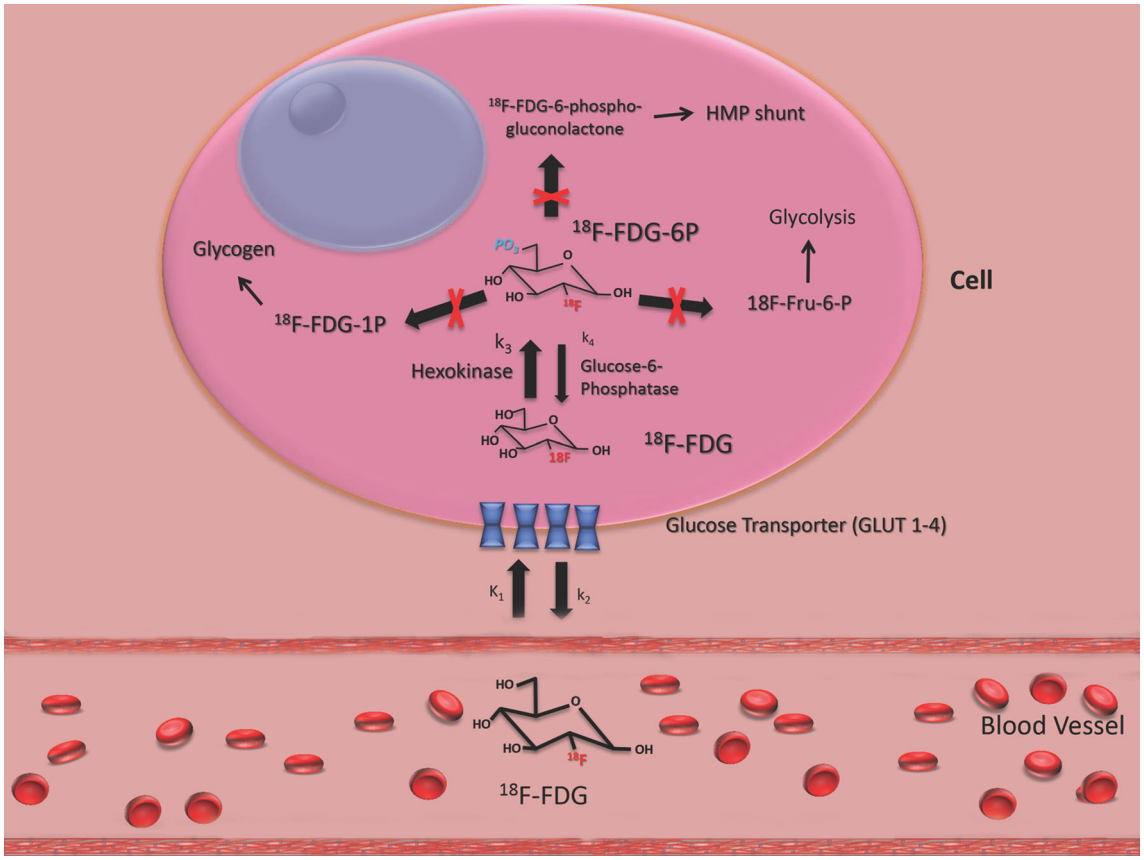



**Fig. 1** The figure above schematically demonstrates the fate of FDG after it enters the cell via cell membrane glucose transporters. Immediately after entering the cell, FDG is phosphorylated to FDG-6-phosphate by hexokinase and, unlike the glucose molecule, cannot be metabolized further. However the fate of FDG-6-phosphate differs in malignant and inflammatory as well as in normal cells. Cancer cells either lack or have low levels of glucose-6-phosphtase and, therefore, FDG-6-phosphate accumulates in the cell continuously over time. In contrast, inflammatory cells are known to have substantial levels of this enzyme, which metabolizes FGD-6-phosphate, and the free FDG released can no longer be retained in the cells and therefore returns to the bloodstream (color figure online)

revealed on second time point images [16, 17]; the opposite occurs in inflammation and infection, due to high levels of glucose-6-phosphatase. It is hypothesized that free FDG, after being separated from phosphate, will leave the cell and become detectable by delayed time point imaging [15]. In addition, high levels of glucose transporters and hexokinase in malignant cells contribute to significant accumulation of FDG in cancer cells over time [2, 18, 19].

The application of DTPI has been investigated by many groups and its potential and limitations [2] have been discussed in detail with reference to a wide variety of malignant diseases including those of the lung [6, 20–24], breast [7, 11, 25–28], head and neck [8, 29], colorectal region [30, 31], brain [32, 33], and lymphatic tissues [3, 34], as well as pediatric cancers [35], gallbladder carcinoma [36]) as well as nonmalignant disorders (atherosclerosis [37, 38], inflammation [39]) and normal states [40, 41] (Table 1). The aim of this review is to describe the role of DTPI in assessing both normal and disease states.

## Normal states: dynamic changes in normal tissues

The degree of FDG uptake and its retention in the cells is highly dependent on a multitude of factors, including tracer distribution time and plasma glucose levels [42]. In addition, the background activity decreases over time with DTPI, therefore the contrast between the target lesion and the surrounding tissues increases [2]. For this reason, standardized uptake values (SUVs) vary depending on the interval that elapses between the administration of FDG and the image acquisition. Currently, no specific time point has been adopted for differentiating benign disorders from malignant diseases. Therefore, to properly interpret PET images, it is essential to have some specific knowledge about the dynamics of FDG at different time points [12, 41].

Normal tissues have different metabolic rates and glycolytic activities and, as in pathological states, the levels of glucose-6-phosphatase and of glucose transporters and hexokinase dictate the dynamics of FDG in various normal tissues. Accordingly, an understanding of the physiological

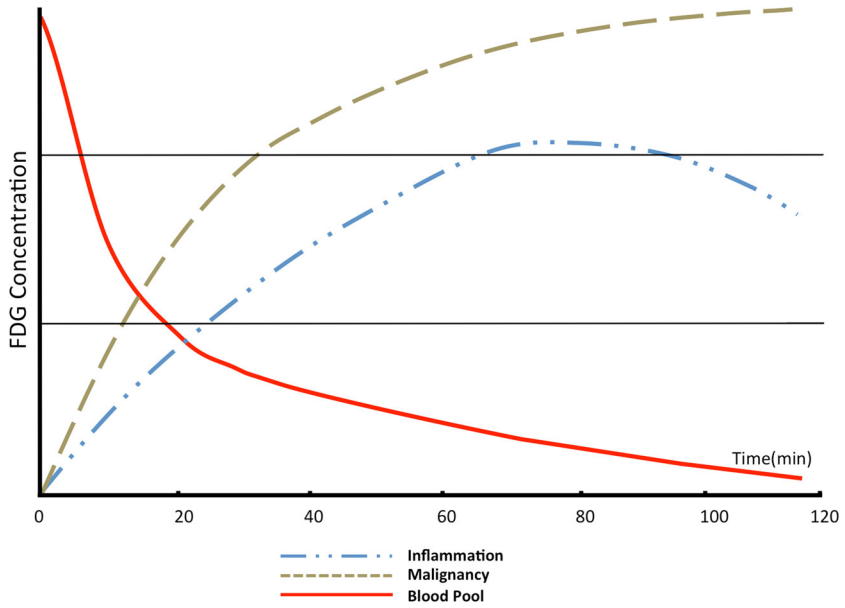



**Fig. 2** Time course of FDG accumulation in malignant and inflammatory cells differs as depicted above. While both are shown to incorporate this radiotracer for a period of time, the pattern is substantially different between the two at later time points. Malignant cells continue to show increasing levels of FDG uptake over time. In contrast, inflammatory lesions either reveal a decline in FDG uptake or plateau off after a certain time course. The decline or plateau is likely due to loss of FDG from the cell following metabolization of FDG-6-phosphate by glucose-6-phosphatase. In malignant cells, on the other hand, because the glucose-6-phosphatase is lacking, FDG-6-phosphate is continuously retained and increases over time. We should point out that blood pool activity decreases exponentially soon after the administration of this compound and therefore, the contrast between target tissues (cancer, inflammation, etc.) increases substantially over time and the lesion becomes more distinct. This phenomenon is more prominent for cancer tissues compared with inflammatory lesions (color figure online)

uptake levels of each tissue type becomes crucial in order to employ appropriate imaging protocols, and particularly to implement DTPI for differentiation of malignant from benign lesions [12, 41].

Cheng et al. [41] determined FDG uptake and clearance in normal tissues in 30 patients examined by PET at 1, 2 and 3 h after the administration of FDG; to do this they measured the $SUV_{max}$ and $SUV_{mean}$ of various normal tissues. The results of this study revealed that blood pool, liver and spleen FDG levels decreased from the first to the second hour and from the second to the third hour, while those of the lungs, pancreas, lymph node and skeletal muscles decreased only between the first and second hour. In contrast, bone marrow FDG uptake values were found to be increased on delayed images. The parotid gland, thyroid gland and prostate did not show any significant changes on delayed imaging. In another study by the same authors, it was further shown that FDG uptake values in the left ventricle increased with delayed time point imaging. This study also confirmed finding of the previous study concerning disproportional degrees of increased FDG uptake in the areas of myocardium with a higher $SUV_{max}$ on the initial scan [40].

Basu et al. [43] prospectively investigated the temporal profile of FDG uptake over periods of up to 8 h in normal tissues as well as in cancerous lesions and reported a trend towards a steady rise in the SUVs of malignant lesions in this time frame, while the SUVs of the normal organs stayed the same or decreased. The authors concluded that delayed imaging over time improves the sensitivity of FDG PET for detecting malignant lesions. They also observed varying slopes of FDG uptake over time, which they interpreted as reflecting tumor heterogeneity and the underlying tumor biology of the lesions examined.

## Differentiating benign from malignant lesions

As noted above, the accumulation of FDG is dependent on many factors. Among these, glucose-6-phosphatase, hexokinase and GLUT transporters appear to be critical ones and should therefore, by means of DTPI, be characterized on the basis of their capacity to differentiate between benign and malignant lesions. Brain and heart tissues both show high levels of FDG uptake, likely due to high levels of GLUT transporters and relatively low levels of glucose-6-phosphatase. Malignant cells also possess considerable numbers of GLUT transporters with a decreased ratio of glucose-6-phosphatase to hexokinase, leading to substantial degrees of FDG accumulation. Different types of

**Table 1** List of studies which implemented dual time point imaging (DTPI)

| References | Clinical setting | *n* | Parameters evaluated | Findings and conclusions |
|---|---|---|---|---|
| Shinozaki et al. [63] | Staging of preoperative lung cancer | 100 | $SUV_{max}$, RI | Early phase FDG PET changed the staging of tumors to an upper level in 10 % and down-staged 5 % of them. The delayed phase did not add further information regarding the staging |
| Cheng et al. [21] | Diagnostic value of serial FDG uptake in malignant versus benign lung lesions | 43 | $SUV_{max}$, RI | 2 and 3 h $SUV_{max}$ similarly outperformed first hour $SUV_{max}$. The optimum cutoff values for malignant benign differentiation were 3.24, 3.67 and 4.21 for 1st, 2nd and 3rd h. Third hour $SUV_{max}$ had the best overall performance with accuracy of 88.8 %. Delayed imaging significantly enhanced the quality of image |
| Garcia Vicente et al. [25] | Nodal staging and staging detection of extra-axillary involvement in breast cancer | 75 | Visual, $SUV_{max}$ | Sensitivity and specificity of visual assessment was 87.3 and 75 %, respectively. Early and delayed $SUV_{max}$ of 0.9 and 0.95 had the best sensitivity for first and second time point, respectively. 1.95 and 2.75 were the most specific values for $SUV_{max}$ at first and second time point, respectively |
| Lee et al. [74] | Differential diagnosis of thyroid incidentaloma | 29 | $SUV_{max}$, RI | SUV at second time point and RI were able to discriminate between benign and malignant thyroid lesions. SUV at the second time point with a cutoff of 3.9 was 87.5 % sensitive and 75 % specific. RI greater than 12.5 % was expected to be malignant |
| Kaneko et al. [22] | Differentiation of benign pulmonary lesions (tuberculous and nontuberculous) and primary lung cancers | 81 | $SUV_{max}$, RI | Benign pulmonary lesions and primary lung cancer lesions both had similar high RIs (mean $\pm$ SD 33.6 $\pm$ 22.6 and 32.5 $\pm$ 23.7, $p = 0.95$). Both tuberculous and non-tuberculous lesions had high RI values. Benign lesions tended to show lower RIs in higher SUVs at first time point while malignant lesions had persistent high RIs without relationship to SUV. No significant difference between malignant and benign lesions |
| Li et al. [64] | Regional nodal staging in non-small cell lung cancer using DTPI for differentiation versus tubercular granulomatous tissues | 39 | RI | Difference in the RI in the benign and malignant lesions was not statistically significant. FDG PET combined with CT attenuation improved the diagnostic specificity and accuracy. DTPI had limited applicability for lymph node differentiation |
| Satoh et al. [61] | DTPI for evaluation of prognosis and risk factors for recurrence in stage I stereotactic body radiation therapy-treated nonsmall cell lung cancer | 57 | $SUV_{max}$, RI | Three-year overall survival was 63.4 %. $SUV_{max}$ did not change any prognostic measure. RI predicted higher numbers of distant metastasis and fewer numbers of local recurrences and regional lymph node metastasis |
| Kim et al. [75] | DTPI for lymph node staging in nonsmall cell lung cancer | 69 | $SUV_{max}$, RI | Delayed $SUV_{max}$ was more accurate than RI and early $SUV_{max}$ in the lymph node-based analysis. DTPI could increase the diagnostic accuracy for lymph node staging of nonsmall cell lung cancer |

**Table 1** continued

| References | Clinical setting | *n* | Parameters evaluated | Findings and conclusions |
|---|---|---|---|---|
| Kim et al. [60] | Prognosis of early stage nonsmall cell lung cancer using DTPI | 66 | $SUV_{max}$, percent change of $SUV_{max}$ | Overall survival and disease-free survival in patients with $SUV_{max}$ below or equal to 5.75 was better than in the group with $SUV_{max}$ above 5.75. Percent change in SUV max did not have prognostic value. $SUV_{max}$ (early and delayed) predicted overall survival. Percent change in $SUV_{max}$ had limited prognostic value |
| Kim et al. [76] | Evaluation of predictive value of DTPI in N1 status in nonsmall cell lung cancer | 70 | $SUV_{max}$, percent change of $SUV_{max}$ | DTPI was not able to predict pathologic N1 status in nonsmall cell lung cancer |
| MacDonald et al. [77] | Evaluation of solitary pulmonary nodules with initial standard uptake below 2.5 | 54 | $SUV_{max}$, RI | DTPI with RI analysis is useful for evaluation of solitary pulmonary nodules with $SUV_{max}$ <2.5. Prolongation of delay time from 120 to 180 min did not add any value |
| Lee et al. [4] | Detection of liver metastasis in colorectal cancer patients using DTPI | 39 | Visual, SUV, tumor-to-liver uptake ratio (TLR), percent changes of SUV and TLR | SUV and TLR of metastatic lesions were higher in the delayed images. Visual analysis detected 77 % of lesions on early and 87 % of lesions on delayed images. DTPI is promising for detection of liver metastasis in colorectal cancer |
| Yoon et al. [31] | Neoadjuvant chemoradiation response of locally advanced rectal cancer | 61 | $SUV_{max}$, RI, dual-point index | RI and dual-point index remained as significant predictors in the multivariate analysis. Delay index was 86.7 % sensitive, 87 % specific with PPV of 68.4 % and NPV of 95.2 % and accuracy of 86.9 %. Dual-point post chemoradiation therapy PET/CT study is a better predictor of pathological tumor as compared to single time point pre- and post-chemoradiation therapy PET/CT |
| Toriihara et al. [78] | Salivary gland tumor characterization | 40 | $SUV_{max}$, RI | No significant difference was noted between early and delayed $SUV_{max}$. Dual time point FDG PET is not useful for this purpose |
| Nakayama et al. [34] | Differentiating lymph nodes between malignant lymphoma and benign lesions | 84 | $SUV_{max}$, difference between early and delayed $SUV_{max}$ (D-$SUV_{max}$), RI | Delayed parameters were significantly higher in malignant lymphoma than in benign lesions. Delayed FDG uptake parameters were useful indices for differentiation of malignant lymphoma from benign lesions |
| Matthiessen et al. [79] | Evaluating dual time point imaging in large loco-regional recurrences following electrochemotherapy of breast cancer | 11 | $SUV_{max}$ | 1 and 3 h delayed imaging is a promising technique for assessment of electrochemotherapy-treated breast cancer recurrences on the skin |
| Costantini et al. [35] | Assessment of DTPI in pediatric malignancies | 21 | $SUV_{max}$, RI | Average SUV increased from 7.3 to 10.9 in malignant cases while it changed from 4.5 to 4.2 in benign lesions. Average RI for malignant lesions was 37.1 % versus −9.9 % for benign cases. Cutoff value of 10 % for RI showed sensitivity and specificity of 77 and 80 % respectively |
| Choi et al. [80] | Differentiating extrahepatic cholangiocarcinoma from benign disease using DTPI | 39 | $SUV_{max}$, percent change of $SUV_{max}$, ratio of $SUV_{max}$ in comparison with average SUV of right hepatic lobe | Significant difference in $SUV_{max}$ 1 in benign and malignant lesions (5.43 T 4.66 vs 2.26 T 0.83, $p = 0.003$). Same results for $SUV_{max}$ 2 (6.02 T 5.26 vs 2.26 T 0.76, $p = 0.002$). No significant difference in other parameters was noted. No added benefit of DTPI was seen |

**Table 1** continued

| References | Clinical setting | *n* | Parameters evaluated | Findings and conclusions |
|---|---|---|---|---|
| Shum et al. [81] | DTPI for assessment of esophageal squamous cell carcinoma | 26 | $SUV_{max}$, RI | Combination of early $SUV_{max} \geq 2.5$ or RI $\geq 10$ % had a sensitivity of 96.2 %, which was the highest. Higher specificity was noted when combination of $SUV_{max} \geq 2.5$ and RI $\geq 10$ % or $SUV_{max} \geq 2.5$ alone was implemented. DTPI had limited value in primary tumor detection and loco-regional lymph node metastasis. RI $\geq 10$ % might improve the sensitivity and specificity of detection of distant metastasis |
| Shinya et al. [3] | DTPI in malignant lymphoma patients | 43 | $SUV_{max}$, RI | $SUV_{max}$ at 2nd hour was significantly higher than at 1st hour. DTPI with semi-quantitative approach might be able to accurately diagnose, stage and predict lymphoma subtypes when compared with STPI |
| Miyake et al. [82] | Clinical value of early delayed scanning (85 min post injection) in comparison with conventional delayed scanning (124 min post injection) in colorectal cancer | 54 | Visual, $SUV_{max}$ | Neither 85 min nor 124 min post injection scan improved the staging of colorectal cancer |
| Lee et al. [30] | Relationship between DTPI and immunohistochemical factors in preoperative colorectal cancer | 47 | $SUV_{max}$, RI | Higher RIs in patients with advanced T stage. Patients with higher levels of GLUT-1 had increased RIs. Patients with increased p53 had slightly elevated RIs when compared with ones without increased p53. T staging was independently correlated with RI. RI has the potential to be used as a prognostic marker |
| Hahn et al. [83] | Axillary lymph node metastasis detection in breast cancer patients using DTPI | 38 | $SUV_{max}$ | The sensitivity, specificity, PPV, NPV and accuracy for detection of axillary lymph node metastasis was not statistically significant at two time points |
| Garcia Vicente et al. [25] | Biological prognostic factors and DTPI in locally advanced breast cancer | 36 | $SUV_{max}$, RI | RI was superior to $SUV_{max}$ values regarding correlation with biological parameters and can be suggested as a prognostic marker |
| Chang et al. [19] | Correlation of DTPI with Ki-67 proliferation index in new cases of non-Hodgkin lymphoma | 27 | $SUV_{max}$, RI | DTPI was shown to be feasible for measurement of tumor proliferation |
| Prieto et al. [33] | DTPI for brain tumor identification and delineation | 25 | SUV, tumor-to- normal gray matter ratio | Quantitative DTPI improves the sensitivity for detection and delineation of advanced brain tumors |
| Kim et al. [84] | DTPI in diagnosis and prediction of incidental thyroid nodules | 50 | Visual, percent change of $SUV_{max}$ | All indices were similar in efficacy for diagnosis and prediction of malignancy |

malignant cells have variable concentrations of glucose-6-phosphatase and therefore show variable time-activity FDG uptake curves. In contrast, it has been speculated that inflammatory cells have higher levels of glucose-6-phosphatase with an increased ratio of glucose-6-phosphatase to hexokinase, which results in breakdown of FDG-6-phosphate and clearance of FDG from the cells over time [44].

## Nonmalignant diseases

### Atherosclerosis

Delayed time point imaging has been used for the visualization of atherosclerotic plaques. Blomberg et al. [37] in their study, determined the ideal time point, following the administration of FDG, for detecting and quantifying the presence and degree of atherosclerotic plaque inflammation by FDG PET/CT. They imaged 15 patients at three time points (1, 2, and 3 h post injection) and assessed aortic and carotid FDG uptake using qualitative and semi-quantitative methods. They noted significantly improved visualization of atherosclerotic plaques on the delayed images. The aortic and carotid mean target-to-background ratios (TBRs) at the first hour were 1.05 (95 % CI 0.98, 1.11) and 0.88 (95 % CI 0.81, 0.96), respectively. At the third hour, they rose to 1.57 (95 % CI 1.28, 1.86; $p = 0.001$) and 1.61 (95 % CI 1.36, 1.87; $p < 0.001$), respectively.

In another study, Blomberg et al. [38] employed DTPI in a prospective study of 40 subjects using FDG PET/CT. FDG parameters were measured on 1.5 and 3 h scans and the results were compared with 10-year risk for fatal cardiovascular disease (SCORE %). The authors found significant increases in the FDG uptake parameters over time in both carotid arteries and in the aorta. The correlation with cardiovascular risk was not significant at the first time point but a significant correlation between the corrected $SUV_{max}$ of the carotid arteries ($\tau = 0.25$, $p = 0.045$) and aorta ($\tau = 0.33$, $p = 0.008$) and SCORE % was found at the second time point (3 h). The authors therefore concluded that delayed time point imaging improves the quantification of atherosclerosis and allows accurate assessment of this major cardiovascular risk factor. These findings demonstrate that over time, with declining background blood pool activity, the contrast between target tissues improves regardless of their underlying disease process (cancer, inflammation, etc.), and the sensitivity of FDG PET in detecting various abnormalities in many organs increases.

### Infectious/inflammatory lung diseases

The role of DTPI has been tested in settings other than those of distinguishing malignant from benign disorders. Umeda et al. [45] assessed differential diagnosis and prediction of disease activity in patients with idiopathic interstitial pneumonitis (IIP). They scanned 50 patients at 1 and 3 h and quantified the SUV and retention index SUV (RI-SUV) for comparison with CT findings. A monthly pulmonary function test was done after FDG PET/CT study to assess disease progression. Early cryptogenic organizing pneumonia (COP) had higher SUVs as compared to idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP). They suggested that the early SUV value might be used as a marker for differentiation of COP from NSIP and IPF. It was also shown that a positive RI-SUV predicts deterioration of lung function in IIP patients. Early SUV and RI-SUV parameters evaluated with DTPI might predict disease progression and treatment response to steroids in IIP patients soon after medical evaluation.

### Pulmonary sarcoidosis

Dual time point FDG PET/CT imaging has also been used for the prediction of disease progression in pulmonary sarcoidosis. Umeda et al. [46] scanned 21 patients with pulmonary sarcoidosis at 1 and 3 h post injection. SUVs and RI-SUVs were calculated and disease progression was evaluated on the basis of a chest CT performed a year after FDG PET/CT. RI-SUVs were significantly higher in patients with increased or unchanged lesions on follow-up CT when compared with patients with lesions showing a lower retention index (RI). RI-SUVs showed greater diagnostic accuracy when compared with the use of early conventional single time point imaging (STPI) SUV measurement and serum soluble IL-2 and $^{67}Ga$ uptake in the group examined. They concluded that RI-SUVs might be used for measurement of persistent inflammation in patients with pulmonary sarcoidosis.

### Crohn's disease

It has been shown that DTPI might also be able to predict potential response to treatment with antitumor necrosis factor (TNF) drugs in patients with Crohn's disease (CD) [47]. In this preliminary study, nine patients with CD were evaluated using DTPI before and after treatment and response to treatment was quantified as the difference between pre-treatment and post-treatment global CD activity and FDG RI between the first and the second hour after the administration of the radiotracer. Treatment response was shown to be correlated with pre-treatment RI with a correlation coefficient of 0.76 ($p = 0.01$), suggesting that pre-treatment RI can be an important predictor of response to anti-TNF therapy. Further studies with larger study samples are needed to define the role of DTPI in CD.

### Brown fat

Brown adipose tissue is a known source of false-positive results in FDG PET studies [48, 49]. Brown fat tissues are visualized as bilaterally elongated and symmetrical structures in the supra clavicular area and are infrequently interpreted as malignant lesions or nodal metastases [50, 51]. Alkhawaldeh et al. [48], implementing DTPI, quantitatively assessed FDG PET scans from 32 patients for hypermetabolic brown fat activity and noted diverse patterns of distribution of brown fat throughout the body including the supraclavicular, cervical, axillary, paravertebral, mediastinal, upper abdominal and intercostal regions. The $SUV_{max}$ ranged from 0.8 to 12.4 at these uptake sites over time. 76 % of the brown fat sites showed increased uptake which ranged from 12 to 192 %, while 13 % did not change and 11 % showed decreased values.

## Malignant diseases

### Lung cancer

#### *Diagnostic performance*

Two-thirds of pulmonary nodules are benign (mostly due to inflammatory reactions) and the rest are malignant in nature [52, 53]. It is now well established that FDG PET is beneficial in the diagnosis and staging of lung cancer lesions [54] (Fig. 3). However, false-positive [9] and false-negative [24] results have been reported in the literature.

Matthies et al. [24] reported sensitivity and specificity values of 80 and 94 %, respectively, for a cutoff SUV of 2.5 on the standard FDG PET scan. In their study, DTPI was found to increase the sensitivity to 100 %, but did not significantly change the specificity of the test (89 %).

Alkhawaldeh et al. [55] in another study using DTPI, found it to improve the diagnostic accuracy of FDG PET in the assessment of solitary pulmonary nodules.

Cheng et al. [21] prospectively assessed dynamic changes in FDG uptake in patients with proven or suspected lung cancer at 1, 2, and 3 h post-injection and concluded that multiple time point imaging moderately improves the diagnostic accuracy of FDG PET in assessing lung lesions. The $SUV_{max}$ of 4.21 at the third hour was found to show the best diagnostic performance (=88 %). The TBR increased over time and the overall quality of the images on the delayed images appeared to be superior to that of the early scans.

Lin et al. [56], in their systematic review and meta-analysis of 11 studies comprising 788 patients, conducted to assess the potential value of dual time point versus single time point FDG PET imaging, found the area under curve for DTPI and STPI to be 0.839 (0.079) and 0.757 (0.074), respectively. Their analysis demonstrated that DTPI may not be recommended for routine clinical use. However, it may provide additional information in specific non-diagnostic settings where STPI is of limited value in characterizing lesions.

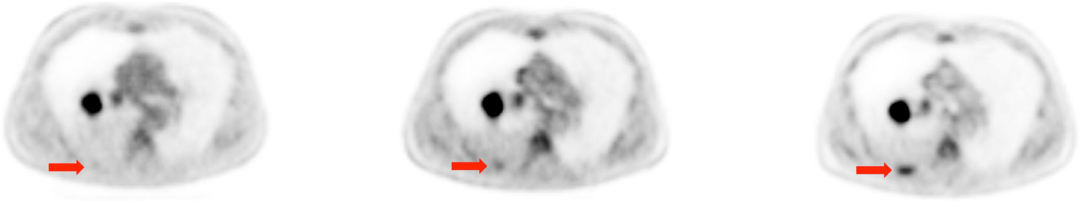
Zhang et al. [57] in their meta-analysis of eight studies (for a total of 415 patients and 430 pulmonary nodules), reported a sensitivity of 79 % (95 % CI 74.0–84.0 %) and a specificity of 73 % (95 % CI 65–79) for DTPI. STPI had a sensitivity of 77 % (95 % CI 71.9–82.3 %) and a specificity of 59 % (95 % CI 0.29–0.49). They concluded that DTPI and STPI with FDG PET show relatively similar accuracy for differentiating pulmonary nodules. However, DTPI appeared, on the basis of this meta-analysis, to be more specific than STPI.

#### *Prognostic performance*

FDG uptake parameters generated from either DTPI or delayed time-point imaging alone can be used for predicting the outcome of lung malignancies. Houseni et al. [58], in their study, reported $SUV_{max}$ changes from 1 to 1.5 h as a strong independent predictive factor for lung cancer prognosis. On the basis of these data a more than 25 % increase in the $SUV_{max}$ predicted significantly shorter overall survival time as compared to that recorded in the group with values that were <25 %. Chen et al. [59] studied the prognostic value of DTPI in patients with nonsmall cell lung cancer by measuring the increment in $SUV_{max}$ ($SUV_{inc}$) between the first and second hour. They noted that the cutoff value of >1 for $SUV_{inc}$ over time had the best prognostic value for progression-free survival. The 3-year progression-free survival and overall survival values were 61.6 and 87.8 % in patients with $SUV_{inc} \leq 1$ versus 21.1 and 46.2 % in patients with $SUV_{inc} > 1$ (all $p < 0.01$). The authors concluded that DTPI provides a promising prognostic value for determining the outcome in nonsmall cell lung cancer.

In contrast, Kim et al. [60] reported that the percentage change in $SUV_{max}$ recorded in DTPI may not predict outcome. The $\%\Delta$ $SUV_{max}$ did not predict overall survival or disease-free survival. However, tumor $SUV_{max}$ in early images was a significant predictive factor for overall survival ($p = 0.0142$) and disease-free survival ($p = 0.0421$) in surgically resected early stage non-small cell lung cancer.

Satoh et al. [61] showed that $SUV_{max}$ is not able to predict recurrence or survival times. In contrast, the RI could detect and determine the number of distant metastatic lesions and, therefore, predict local recurrence rates and regional lymph node metastasis.




d

| Lesion | 1 | 2 | 3 |
|---|---|---|---|
| Primary lesion MTV | 6.9 | 6.9 | 7.4 |
| Primary lesion SUVmax | 11.5 | 13.5 | 16.2 |
| Primary lesion TLG | 48.2 | 54.1 | 70.5 |
| Right pleural lesion - MTV | 8.2 | 11.1 | 15.8 |
| Right pleural lesion - SUVmax | 1.7 | 3.3 | 5.4 |
| Right pleural lesion - TLG | 9.9 | 25.7 | 55.8 |

**Fig. 3** The images above (**a**, **b**, **c**) demonstrate the importance of delayed imaging in assessing the degree of aggressiveness of the primacy malignant lesion but also in improving the sensitivity of the technique for detecting regional and distant metastatic sites. In this patient with lung cancer, the primary lesion was found to show a substantial rise in the degree of FDG uptake, both qualitative and quantitative, over time. In addition, pleural involvement on the same side was undetectable in the images acquired at 1 h after administration of FDG but became visible over time and appeared very intense at 3 h (*arrows*). The table (**d**) further confirms this observation by providing quantitative values for both the primary lesion and the involved pleura. The table provides conventional and novel quantitative measurements (*MTV* metabolic tumor volume, *TLG* total lesion glycolysis, $SUV_{max}$, maximum standardized uptake value) (color figure online)

*Lymph node staging of lung cancer*

Dual time point imaging (DTPI) has been studied as a means of detecting of lymph node metastasis in lung cancer. Accurate detection of lymph node metastasis is crucial for treatment planning. Shen et al. [62], in their meta-analysis, evaluated the diagnostic performance of DTPI and STPI with FDG PET for the detection of mediastinal nodal metastasis in non small cell lung cancer. DTPI with FDG PET performed slightly better than STPI with FDG PET in the evaluation of mediastinal lymph nodes. However, due to the small sample of patients and the heterogeneity of the population examined, future studies should be carried out to determine what role DTPI might play for this purpose.

Shinozaki et al. [63] examined the diagnostic accuracy of DTPI versus STPI with FDG PET in the pre-operative staging of lung cancer in 100 patients. Early time point imaging with FDG PET resulted in upstaging of the tumor in 10 % and down staging of the tumor in 5 % of the cases. However, DTPI did not appear to add any additional information to the overall staging of the lung cancer patients. This finding suggests that although DTPI is useful for differentiating between malignant and benign lesions, overall it has no major impact on the staging and management of patients with lung cancer.

## Breast

FDG PET has been used for diagnosing and staging breast cancer and for detecting recurrence of the disease. Most breast cancers are low-grade malignancies and small in size in many patients and these are two of the factors that limit the applicability of FDG PET in this malignancy [44]. Mavi et al. [11, 15] studied DTPI in a relatively large number of breast cancer patients. Their study included 152 patients scanned twice with a mean interval of 52 min between the two images. They observed an increase in FDG uptake over time in malignant lesions when compared with normal breast tissue. They also noted that changes in FDG uptake at different time points may reflect the tumor biology and the degree of aggressiveness of the malignant lesion.

Caprio et al. [28] assessed the diagnostic performance of DTPI in suspected breast cancer lesions. They studied 59 patients at 1 and 3 h after FDG injection, qualitatively and semiquantitatively evaluating the changes in FDG uptake parameters and comparing them with the results from histopathological examinations of the excised lesions. DTPI showed an accuracy of 85 % for the lesions with $SUV_{max}$ above or equal to 2.5 and/or positive percent change in $SUV_{max}$. This parameter had a sensitivity of 81 % and a specificity of 100 %, when compared with accuracy, sensitivity and specificity values of 69, 63, and

100 % in STPI, respectively. They concluded that DTPI, when compared with STPI alone, improves the breast cancer detection accuracy in patients with suspicious lesions.

### Head and neck

Generally there is a considerable degree of physiological FDG uptake in the head and neck region. Furthermore, episodes of inflammation and infections in the upper respiratory tract result in increased FDG uptake in the affected sites. Radiation-induced inflammation is also a leading cause of false-positive FDG uptake in head and neck cancers. DTPI has been employed in this setting to determine its role in evaluating the complex anatomical structures of this region and the preliminary results, with regard to the differentiation of benign and malignant lesions, appear to be promising [44].

Hustinx et al. [8] used DTPI for the assessment of head and neck lesions and noted that while SUV levels were similar in tumors and inflammation on baseline scans, over time, FDG uptake in the tumors increased by 30 % whereas uptake in inflammatory or normal tissues remained stable.

Abgral et al. [29] prospectively investigated the independent prognostic value of DTPI with FDG PET in patients with head and neck squamous cell carcinoma at 1 and 2-h image acquisition. The intra-tumoral RI was measured. Event-free survival and overall survival were compared with $SUV_{max}$ at different time points. Age, stage and RI were predictive of event-free survival ($p = 0.01$) only. $SUV_{max}$ at 1 h was not predictive of event-free survival or overall survival. At the second time point, $SUV_{max}$ was predictive of overall survival, but not event-free survival. On multivariate analysis, the RI emerged as the only predictive factor for event-free survival.

### Limitations

Dual time point imaging (DTPI) has certain limitations, which makes its utility in routine clinical practice somewhat unclear at this time [2]. The use of DTPI to differentiate between inflammatory and malignant lesions has not been consistently successful in every setting, as discussed in this review. A number of studies have shown a significant non-specificity of this approach for differentiating between benign and malignant lesions, especially, in the lung and mediastinal regions [13, 46, 64–68] and in lung nodules with low FDG avidity [69]. FDG uptake in acute inflammatory lesions, particularly those related to granulomatous/infectious lesions, mimics a pattern seen in malignant lesions [70, 71]. For example, DTPI, when used in tuberculosis-endemic regions or areas with a high prevalence of sarcoidosis, has not shown additional value over STPI [13, 46, 64–68, 72]. Conversely, in chronic inflammatory (and infectious) foci whose FDG uptake shows a decline after a certain time point, metabolically active cells appear to retain FDG-6-phosphate in a manner similar to that of malignant cells. The discrepancy in the results between acute and chronic inflammatory lesions is likely related to the biological behavior of inflammatory cells in these two different settings [2]. Therefore, it is our belief that DTPI can be used for differentiation of malignant from chronic inflammatory sites. Brown fat tends to accumulate FDG over time and can be considered as a confounding factor in DTPI [48]. Some concerns have been raised about DTPI-based evaluation of suspicious focal abdominal FDG uptake, likely due to methodological problems in the studies [44, 73].

### Summary

DTPI methodology has been shown to provide useful diagnostic and prognostic information in certain situations, which may improve the sensitivity, specificity and accuracy of FDG PET studies. Although further, large-scale multicenter studies are required to determine the definitive value of DTPI for use on a routine basis, this approach can already be used in specific settings and conditions in which promising results have been reported.

**Conflict of interest** The authors of this review article (Sina Houshmand, Ali Salavati, Sandip Basu, Benjapa Khiewvan, Abass Alavi) declare that they have no conflict of interest.

**Human and Animal Studies** The manuscript does not contain any studies with human or animal subjects performed by any of the authors.

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