PET/CT to optimize treatment management of high-risk stage III and IV melanoma

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CHAPTER 1

Introduction

INTRODUCTION

Melanoma is the most aggressive and lethal form of skin cancer, ranking among the most common cancers worldwide, with its incidence steadily increasing (1). In 2023, the Netherlands reported nearly 8,500 new melanoma diagnoses and over 800 deaths, making melanoma one of the malignancies with the highest increasing incidence rates in the country (Dutch tumor registry [IKNL], www.iknl.nl).

Melanoma-specific survival is contingent upon the stage of the disease. According to the American Joint Committee on Cancer (AJCC) 8th edition, the 5-year and 10-year melanoma-specific survival rates for all patients stratified by pathological stage is 98% and 95% respectively, for patients with stage I, while these rates declines to 77% and 69%, respectively, for patients with stage III (2). Until recently, once diagnosed with metastatic stage IV melanoma, median overall survival (OS) was only 6 to 7.5 months and with a 5-year OS rate of less than 10% (3, 4).

With the introduction of immune checkpoint inhibitors (ICIs) and targeted therapies combining BRAF and MEK inhibitors (BRAF/MEKi), the treatment landscape for melanoma has undergone a revolutionary transformation over the past decade (5). Phase 3 trials demonstrated for the first time long-term OS of ICI (ipilimumab, nivolumab, pembrolizumab, and the combination of ipilimumab and nivolumab) (6-8). In melanoma patients harboring BRAFV600E/K mutations, targeted therapy with BRAF/MEKi (combinations of dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) demonstrated significant tumor regression and improved survival (9-11).

Targeted therapy in Stage III and IV Melanoma

MAPK pathway and BRAFV600E/K mutation

Mutated BRAFV600 leads to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, which promotes tumor growth, cell proliferation, and metastasis (12, 13), see **Figure 1**. However, BRAFV600E/K mutations are found in only 50-60% of melanomas (14, 15). Although immunotherapy is the preferred first-line treatment, BRAF/MEKi is considered for aggressive, symptomatic advanced melanoma. Therefore, determining BRAF mutation status is crucial for clinical decision-making in these patients.

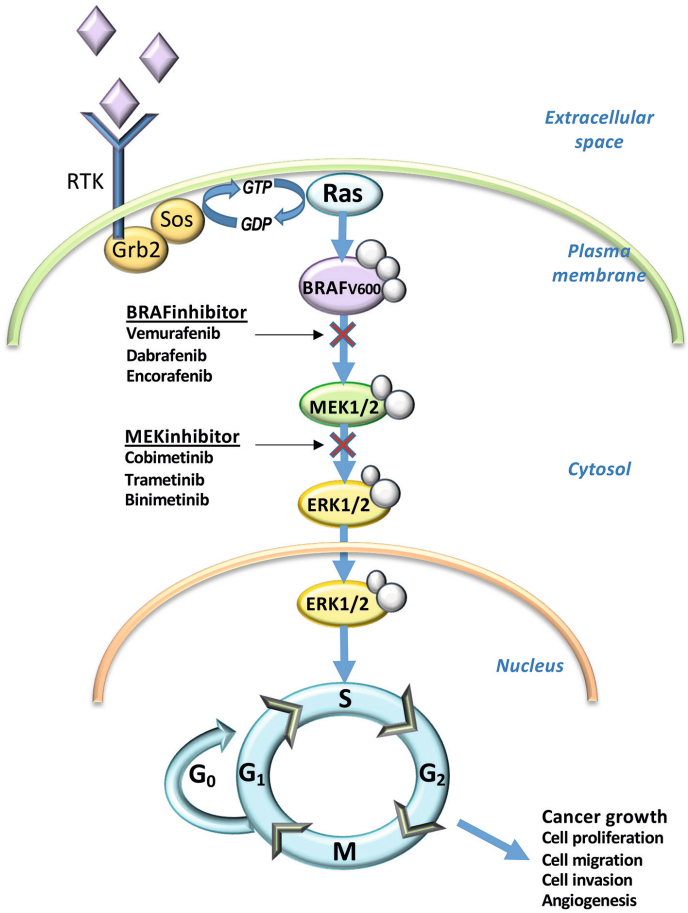

Figure 1. *MAPK signaling pathway. Schematic overview depicting activation of mutated RAF (BRAFV600) within the MAPK signaling pathway. Receptor tyrosine kinases (RTK) receive signaling from ligands (indicated by purple diamond shapes), which then physiologically begin a signaling cascade that passes through RAS, RAF, MEK, ERK, and into the nucleus to impact cell proliferation and survival. The uncontrolled activation caused by mutated RAF (BRAFV600) can be inactivated by a combination of a BRAF inhibitor plus MEK inhibitor.*

Targeted therapy in postoperative settings

Patients with stage IIIB-D melanoma faced a high risk of recurrence and mortality, even after complete tumor resection (2). Until 2010, recurrence detection primarily aimed at surgically removing the disease to prevent progression to unresectable stage III or IV melanoma, as the prognosis for advanced-stage patients was typically very poor. The impact of targeted therapy with combined BRAF/MEKi has emphasized the need for early recurrence detection, therapy monitoring, and resistance prediction in melanoma patients treated with BRAF/MEKi. In the adjuvant setting, ICIs and BRAF/MEKi have significantly improved relapse-free survival (RFS) in stage III melanoma following complete resection, though in a recent study of nearly 10 years of follow-up, no significant benefit was found in OS between BRAF/MEKi dabrafenib plus trametinib and placebo (16-19). The advancements in RFS have heightened interest in the early detection of recurrences, as early intervention can significantly improve patient outcomes. Notably, many recurrences occur within the first 2 years post-surgery (20). Since treatment is more effective when the tumor is still resectable, tumor burden is relatively low and brain metastases are absent, identifying recurrent disease at an early stage may improve patient survival (21-23).

BRAF/MEK inhibitors as neoadjuvant systemic therapy

For patients with unresectable stage III/IV BRAF-mutated melanoma patients, BRAF inhibitors have demonstrated substantial tumor shrinkage, even shortly after treatment initiation. When combined with MEK inhibitors, even higher objective response rates of around 65% have been reported (24-27). These remarkable responses to therapy have driven growing interest in the use of BRAF/MEKi as neoadjuvant systemic therapy (NAST), particularly in cases of borderline resectable or unresectable stage III or oligometastatic melanoma. Several studies have demonstrated that sufficient tumor downsizing through NAST can enable radical resection of previously unresectable locally advanced or oligometastatic disease (28-30). Predicting recurrence before surgery could help personalize post-surgical monitoring, optimizing follow-up strategies for individual patients.

Disseminated melanoma beyond surgery

For patients with advanced BRAF-mutated melanoma who present with symptomatic high tumor burden, treatment with BRAF/MEKi is often indicated to reduce tumor burden. In these patients, clinical trials have demonstrated that BRAF/MEKi therapy offers significant survival benefits over BRAF inhibitor monotherapy in V600E/K BRAF-mutated melanoma (9-11). However, despite high initial response rates, most patients eventually develop acquired resistance, leading to disease progression. The ability to predict response duration could facilitate treatment optimization by transitioning patients to alternative therapies, such as ICIs, before resistance develops. Furthermore, severe adverse events associated with BRAF/MEKi occur in over one-third of patients, sometimes leading to treatment discontinuation (10, 31). Therefore, precise patient

selection to identify those most likely to achieve a durable response with BRAF/MEKi therapy is important.

[^{18}F]FDG PET Imaging to Optimize Targeted Therapy Strategy

Detecting early recurrence

Metabolic imaging using 18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography ([^{18}F]FDG PET/CT) is a non-invasive technique that visualizes glucose metabolism. Since melanoma tumor tissue typically exhibits high [^{18}F]FDG uptake, [^{18}F]FDG PET/CT has proven to be a valuable tool for both primary staging and restaging of melanoma, often influencing treatment decisions (32-34). An example of an [^{18}F]FDG PET/CT of a patient with melanoma metastases is demonstrated in **Figure 2**.

Following complete resection of localized stage III or IV melanoma**,** approximately 10-15% of patients experience disease progression within 12 weeks before initiating adjuvant therapy (16, 35). In such cases, [^{18}F]FDG PET/CT may provide additional value by detecting early recurrent disease. Identifying recurrence at this stage—when the tumor remains resectable or the tumor burden is still low—enhances the effectiveness of immuno- and targeted therapies, which may improve patient survival. Furthermore, the ability to predict recurrence before surgery could enable a more personalized approach to postoperative monitoring.

Monitoring response and resistance prediction

Key prognostic biomarkers for progression-free survival (PFS) and OS in patients with unresectable stage III or metastatic stage IV melanoma undergoing BRAF/MEKi therapy include baseline lactate dehydrogenase (LDH) levels, Eastern Cooperative Oncology Group (ECOG) performance status, the number of affected organ sites and the presence of brain metastases (10, 21, 36). During BRAF/MEKi treatment, melanoma metastases exhibit a rapid and uniform decline in glucose metabolism, reflected by decreased [^{18}F]FDG uptake compared to baseline scans (37). As a result, [^{18}F]FDG PET/CT has gained recognition as a valuable imaging tool for assessing treatment response in BRAF-mutated melanoma (38). Several studies suggest that a reduction in [^{18}F]FDG uptake serves as a prognostic marker for PFS and OS in these patients, supporting its potential role in risk stratification, treatment optimization, and therapy monitoring (37, 39-42).

Quantitative measures of response assessment

Standardized Uptake Value (SUV) is the primary quantitative metric used in PET for assessing radiotracer uptake in tumors, reflecting metabolic activity (43). These SUV parameters are critical in oncology for tumor characterization, treatment response assessment, and prognostic evaluation. Several SUV metrics are commonly used, including SUVmax, SUVmean, and SUVpeak, see **Figure 3**.

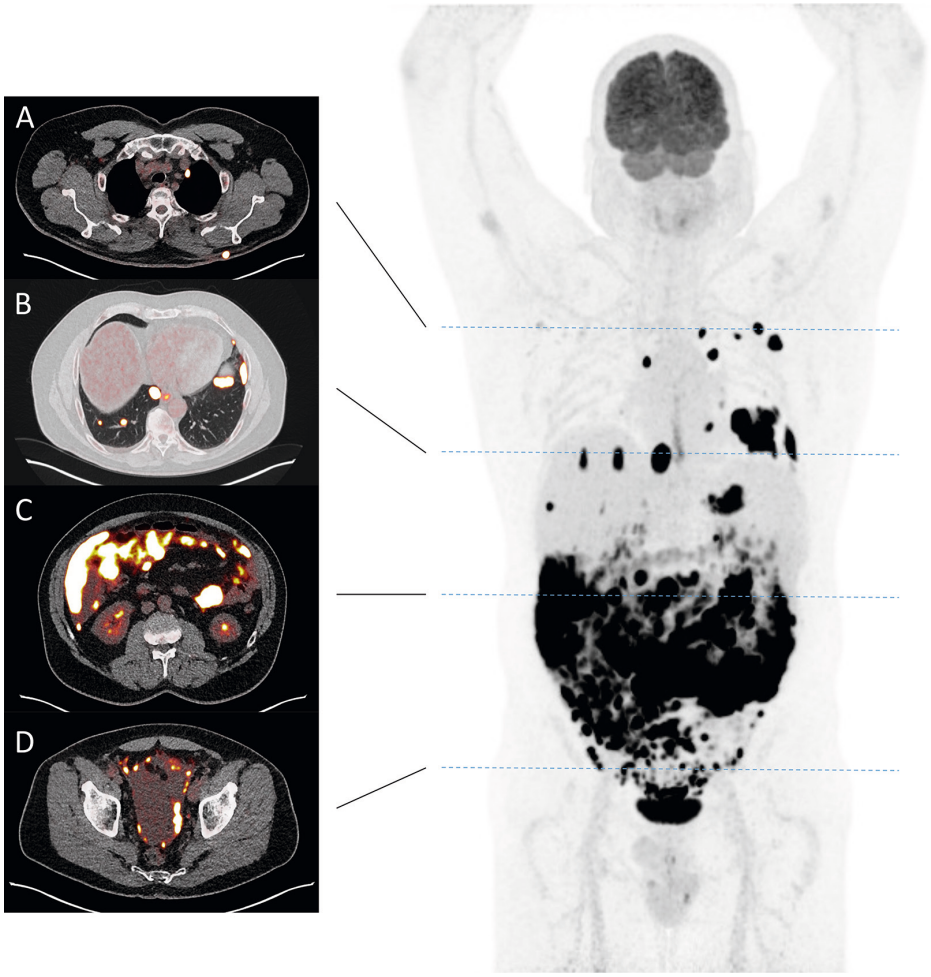

Figure 2. *[^{18}F]FDG maximum intensity projection (MIP) with fused transaxial images (A-D) of a patient with melanoma metastases. The metastases show high [^{18}F]FDG uptake, making even the smallest lesions visible on PET/CT. Transaxial images demonstrate metastases in subcutis (A), lungs (A-B), pleura (B), omentum (C), intestine (C) and peritoneum (C-D).*

SUVmax represents the highest voxel intensity within a region of interest (ROI) and is widely used for its simplicity and reproducibility, though it may be susceptible to noise. SUVmean calculates the average uptake within the ROI, providing a more stable measurement but potentially underestimating focal high-uptake areas. SUVpeak accounts for a small, user-defined region with the highest uptake, offering a balance between SUVmax and SUVmean by reducing noise effects while maintaining sensitivity.

However, SUV is typically normalized to total body weight, making it susceptible to variations in body composition, particularly in overweight or obese patients, where excess adipose tissue - metabolically inactive in [^{18}F]FDG - can lead to overestimated

values. Standardized Uptake Value normalized to Lean Body Mass (SUL), on the other hand, provides a more accurate reflection of metabolic activity by reducing the impact of excess fat. This makes SUL particularly useful in oncologic imaging and treatment response assessment, where consistent and reliable quantification is crucial. As a result, SUL is often preferred over SUV in clinical guidelines, such as PET Response Criteria in Solid Tumors (PERCIST), which quantifies uptake in the most metabolically active lesion at each imaging time point (44). Although response criteria as PERCIST ensures more standardized and reproducible measurements across patients with varying body compositions, visual interpretation of progressive or recurrent disease on [^{18}F]FDG PET/CT remains challenging, particularly in melanoma, which exhibits unpredictable dissemination patterns. While new [^{18}F]FDG-avid lesions often indicate recurrence (45-47), clinical experience suggests frequent false-positives when known tumor lesions remain in remission during BRAF/MEKi therapy.

SUV measurements can be influenced by factors such as body weight, blood glucose levels, and imaging timing (48). To address these limitations, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have emerged as alternative metrics for more comprehensive tumor assessment of several cancers (49-51). MTV quantifies the total volume of metabolically active tumor tissue, offering a broader perspective on tumor burden and biological behavior, while TLG integrates MTV with metabolic intensity (SUVmean×MTV), see **Figure 3**. Emerging evidence suggests MTV may serve as a predictive marker in various cancers, including melanoma patients undergoing BRAF/MEKi therapy (39, 42).

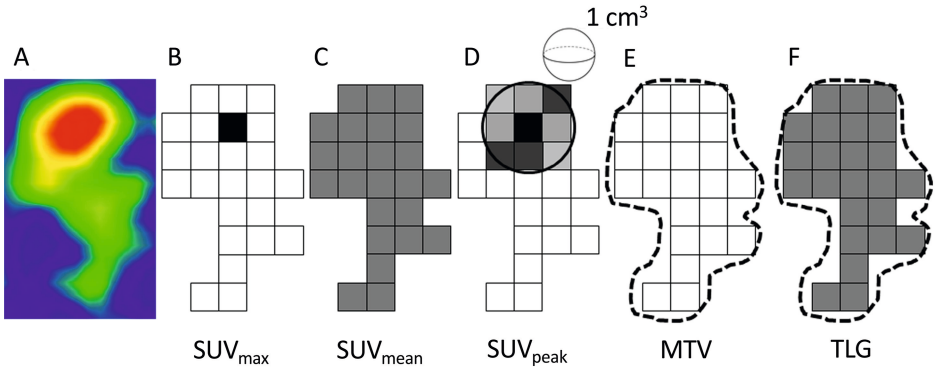

Figure 3. *Schematic overview of different SUV (A-D) and volume-based (E-F) metrics commonly used to quantify radiotracer uptake. (A) Snapshot of lesion with positive radiotracer uptake, e.g. [^{18}F]FDG. (B) SUVmax: voxel with highest uptake within the lesion. (C) SUVmean: average of all SUV values from included voxels within the lesion. (D) SUVpeak: average value within a 1cm^3 sphere surrounding the SUVmax. (E) MTV: volume of increased uptake within the lesion borders. (F) TLG: SUVmean and MTV within lesion borders multiplied providing both metabolic and volume-based information. SUV=standardized uptake value; MTV=metabolic tumor volume; TLG=total lesion glycolysis. Figure adapted with permission from van Dijken et al. (52).*

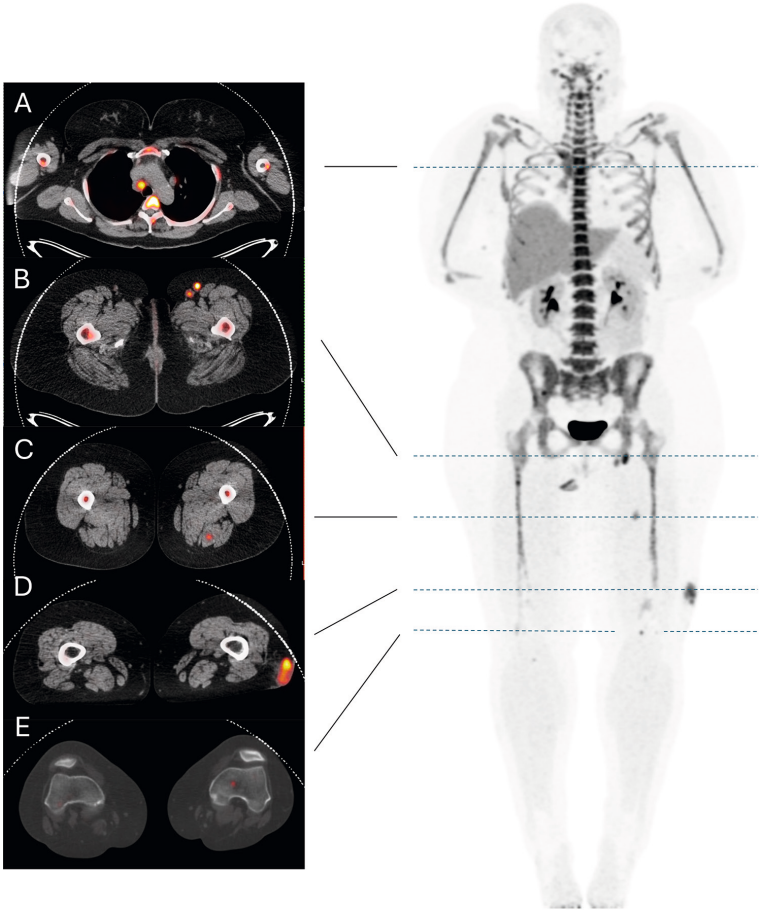

Figure 4. *[^{18}F]FLT maximum intensity projection (MIP) with fused transaxial images (A-E) of a patient with melanoma metastases. Notice the relatively high physiologic uptake in bone marrow and liver, reflecting actual cell proliferation and [^{18}F]FLT being broken-down into plasmabound, respectively. Moderate [^{18}F]FLT uptake is seen in mediastinal (A) and inguinal (B) lymph node metastases and in an intramuscular (C), a subcutaneous (D) and a bone metastasis (E).*

[^{18}F]FLT PET as a Non-Invasive Biomarker for Proliferation

An alternative radiotracer of potential interest, though less frequently used, is [18F]Fluorothymidine ([^{18}F]FLT). As a structural analog of the nucleoside thymidine, [^{18}F]FLT undergoes phosphorylation by thymidine kinase 1 (TK-1) but is not integrated into DNA. Instead, it becomes sequestered within cells during the S-phase of the cell cycle, allowing it to serve as a marker for cellular proliferation, see **Figure 4** (53). As mentioned earlier, BRAF/MEK inhibition blocks aberrant MAPK signaling, halting cell proliferation and tumor growth (54). Previous studies have demonstrated that [^{18}F]FLT uptake correlates with treatment response and Ki-67-measured proliferation, including

in preclinical models (55-58). In vivo imaging of tumor proliferation could enhance routine scans by providing prognostic insights and facilitating response monitoring during BRAF/MEKi therapy (59). As [^{18}F]FLT uptake reflects DNA synthesis, it may better indicate tumor aggressiveness and treatment response than [^{18}F]FDG, with fewer false positives from inflammation (60). Thus, [^{18}F]FLT PET could complement [^{18}F]FDG PET for more precise treatment planning and monitoring (61). However, the impact of tumor burden on the biodistribution of [^{18}F]FLT in healthy tissues, with relatively high physiologic uptake in liver and bone marrow, as well as the rapid alterations in volume and metabolism following BRAF/MEKi treatment, is unclear.

THESIS OUTLINE

This thesis explores the use of [^{18}F]FDG PET/CT to optimize treatment strategy in high-risk stage III and IV melanoma, focusing on its role in the neoadjuvant and postoperative setting and in predicting treatment response to targeted therapy, in which also the additive value of [^{18}F]FLT PET/CT is explored. These topics are further discussed in four Sections.

The first Section focuses on integration of [^{18}F]FDG PET/CT in neoadjuvant and postoperative settings. **Chapter 2** investigates the value of [^{18}F]FDG PET/CT to detect early recurrence after complete resection of high-risk stage III melanoma patients in two cohorts: Cohort 1 (n=35) focused on surveillance in asymptomatic patients (before approval and reimbursement of adjuvant therapy) and patients were assigned to 5x [^{18}F]FDG PET/CT's after surgery: one every 6 months for 2 years, with one final scan after 3 years. Cohort 2 (n=42) was assigned to one screening [^{18}F]FDG PET/CT, which took place in between surgery and the start of adjuvant treatment. **Chapter 3** describes the study in which twenty patients with unresectable locally advanced stage III melanoma were enrolled and were treated with neoadjuvant BRAF/MEKi followed by resection. The potential of [^{18}F]FDG PET/CT was investigated to determine whether it a) could predict histopathological response or recurrence and b) could detect early recurrence after resection.

The second Section evaluates the main objective of the REPOSIT study: determining whether the metabolic response to treatment with the BRAF/MEK inhibitors vemurafenib and cobimetinib during the first 7 weeks, as assessed by [^{18}F]FDG PET/CT, can predict resistance in patients with advanced BRAF-mutated melanoma. The full study protocol is described in **Chapter 4**. Between March 2015 and February 2019, this phase II, open-label, multicenter study recruited 75 patients with histologically proven BRAF-mutated unresectable stage IIIC or stage IV melanoma from nine hospitals that are part of the Dutch Melanoma and Skin Cancer Group (DMSCG). Patients were treated with BRAF/MEKi until progression. Prior to, during treatment and at progression patients underwent [^{18}F]FDG PET/CT and in a subset of patients additional [^{18}F]FLT

PET/CT was performed. **Chapter 5** presents the initial results of the REPOSIT study, analyzing a) whether early response monitoring using PERCIST predicts PFS and b) the dissemination patterns at progression through a lesion-based evaluation compared to baseline, to enhance our understanding of [^{18}F]FDG PET/CT during BRAF/MEKi therapy. In **Chapter 6**, the predictive value of various metabolic PET parameters on [^{18}F]FDG PET/CT are assessed to determine whether these parameters could serve as indicators for PFS. For this, imaging analysis measured baseline SUVpeak, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of summed metastases, as well as percentage changes in these metrics over time.

In the third Section, we explore the proliferation PET imaging biomarker [^{18}F]FLT. In **Chapter 7**, the biodistribution of [^{18}F]FLT PET/CT is evaluated in 18 advanced melanoma patients before and during treatment with BRAF/MEKi. [^{18}F]FLT accumulation in normal liver, bone marrow, blood, and muscle was quantified and inter- and intrapatient variability was analyzed. The study described in **Chapter 8** investigates the potential of [^{18}F]FLT PET/CT in predicting resistance to BRAF/MEKi in stage IV BRAF-mutated cutaneous melanoma patients. To address the study's objective, four distinct analyses were performed: a) a visual comparison of baseline [^{18}F]FLT uptake with [^{18}F]FDG PET/CT was conducted to evaluate differences in imaging characteristics, b) [^{18}F]FLT uptake was compared with Ki-67 expression to assess its correlation with this histopathological tumor proliferation marker, c) a semi-quantitative analysis of baseline [^{18}F]FLT uptake was performed to quantify initial tumor activity, and d) the percentage change in [^{18}F]FLT uptake at Day 14 relative to baseline was analyzed to explore early treatment-induced changes in tracer uptake.

The last Section contains the summary, discussion and future perspectives, and appendices.

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