J of Nuclear Medicine Technology, first published online December 24, 2020 as doi:10.2967/jnmt.120.249540

PET/CT in the evaluation of hypoxia for radiotherapy planning in head and neck tumors: systematic literature review

Susana Lopes[1], Sara Ferreira[2], Marco Caetano[3]

[1] lopesusana686@gmail.com, Nottingham University Hospitals, United Kingdom/ Hucknall Rd, Nottingham NG5 1PB; [2] saramaferreira@ipcb.pt, Health School Dr. Lopes Dias- Polytechnic Institute of Castelo Branco/ Av. do Empresário, 6000-767 Castelo Branco, Portugal; [3] marcuscaetanus@gmail.com, Lisbon School of Health Technology-Polytechnic Institute of Lisbon/ Av. Dom João II Lote 4.69.01, 1990-096 Lisboa, Portugal

Abstract

Introduction: PET/CT combines the molecular with the anatomical level which, with the administration of a hypoxia-sensitive radiopharmaceutical, allows the evaluation of tissue oxygenation.

Materials and methods: The work consists of a systematic literature review, including electronic addresses, books and articles dated from July 1997 to December 2019. The aim of this work is to identify the best suited PET radiopharmaceuticals for the detection of cell hypoxia and recognize the benefits for treatment planning with IMRT/VMAT techniques.

Results: Hypoxia affects the likelihood cure of head and neck tumors, thereby reducing the success rate. Radiopharmaceuticals such as ^{18}F-FMISO, ^{18}F-FETNIM and ^{18}F-HX4 allow the delineation of hypoxic subvolumes within the target volume to optimize IMRT/VMAT treatment.

Discussion: The identification of hypoxia areas with PET/CT imaging and subsequent treatment with IMRT/VMAT allows a possible radiation dose escalation in radioresistant subvolumes.

Conclusion: There is a decrease in relapses and an increased likelihood of disease-free survival.

Palavras-chave

Hypoxic cells
PET/CT
Head and Neck Tumors
Treatment Planning
Radiotherapy

Abreviaturas, siglas e acrónimos

^{18} F-*Fluorine -18*
^{18}F-FMISO-*Fluorine-18-fluoromisonidazole*
^{18} F-HX4- *Fluorine-18-3-fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol*
^{18}F-EF5-*2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-Fluorine-18-pentafluoropropyl)-acetamide*
^{18}F-FAZA-*Fluorine-18-fluoroazomycin arabinoside*
^{18}F-FETNIM-*^{18}Fluorine-labeled-fluoroerythronitroimidazole*
^{18}F-FPIMO-*Fluorine-18-labelled pimonidazole*
^{18}F-RP-170-*Fluorine-18-(1-(2-1-(1H-methyl).ethoxy)-methyl-2-nitroimidazole*
^{62} Cu- *Copper-62*
^{62}Cu-ATSM-*Copper-62-(II)-diacetyl-bis (N4-methylthiosemicarbazone)*
^{64} Cu- *Copper-64*
^{64}Cu-ATSM-*Copper-64-(II)-diacetyl-bis (N4-methylthiosemicarbazone)*
Bq- Becquerel
BTV- Biological Tumor Volume
CT- Computed Tomography
Cu- Copper
FDA-Food and Drug Administration
GTV- Gross Tumor Volume
IMRT-Intensity Modulated Radiation Therapy
mmHg- millimeter of mercury
PET/CT-Positron Emission Tomography/ Computed Tomography
PET-Positron Emission Tomography
SUV- Standard Uptake Value
VMAT-VoluMetric Arc Therapy

Introduction

Positron Emission Tomography/Computed Tomography (PET/CT) as a hybrid imaging technique plays an important role in radiotherapy treatment planning (*1,2*). This technique allows the identification of metabolism, cell proliferation and hypoxia allied to the anatomy (*1,3-5*). After obtaining the PET/CT images for radiotherapy planning and subsequent identification of hypoxic areas, Intensity Modulated Radiation Therapy (IMRT)/VoluMetric Arc Therapy (VMAT) can be used, two conformal treatment techniques that allows to modulate the radiation deposited according to oxygenation levels, decreasing the likelihood of toxicity in adjacent healthy tissues *(6-10)*.

In head and neck tumors, which include the paranasal sinuses, oral and nasal cavity, salivary glands, tongue, larynx, and pharynx, the use of this imaging technique for radiotherapy planning using specific radiotracers, allows precise definition of the hypoxic areas and consequently a more individualized treatment (*11-13*).

In Portugal, in the year of 2010, head and neck tumors were more common in males compared to females. Of all head and neck tumors, the ones of the larynx, demonstrated the highest incidence and mortality rates, being considered the ninth most common tumor in males. In addition to the larynx, tumors in the tongue and oral cavity also have a high incidence and mortality rates (Table 1)*(14)*. Given the low survival rate in head and neck cancers, there is a need to invest in appropriate therapy and, to this end, technological developments have enabled the optimization of the planning and treatment technique. As tumor hypoxia is a poor prognostic factor given the radioresistance of hypoxic cells, it is essential to identify it (*8,15-17*). Therefore, PET/CT for radiotherapy planning taking into account the evaluation of hypoxia, seems a viable option.

Materials and methods

This paper is a systematic literature review that resulted from the bibliographic consultation on PET/CT imaging demonstrating hypoxia, head and neck tumor treatment planning with PET/CT and treatment of

head and neck tumors with IMRT/VMAT. Sixty-eight references were included (Figure 1), namely websites, articles and books, searched in the PubMed, b-on, google and google academic databases in Portuguese and English, dated from July 1997 to December 2019. The following boolean logic was used to search for information: radiotherapy planning treatment AND hypoxia; Hypoxic cells AND radiotherapy treatment AND PET; PET/CT AND hypoxia cells AND treatment; PET/CT AND hypoxia cells AND radiotherapy; PET/CT AND cancer AND hypoxia cells; planning with PET/CT and hypoxia, and also radiotherapy and treatment planning.

This paper aims to answer the following questions:

- How does tumor cell oxygen influences treatment?
- Does the entire target volume need the same radiation dose?
- How important is PET/CT in evaluating hypoxia for treatment planning of head and neck tumors?
- What radiopharmaceuticals to use and why?
- Can the radiation dose to the organs at risk be reduced in an IMRT/VMAT treatment by performing PET/CT planning with hypoxia sensitive radiotracers?

This article aims to contribute to the knowledge and applicability of the PET/CT in the evaluation of hypoxia and to understand the usefulness/contribution to the treatment planning with IMRT / VMAT techniques in patients with head and neck tumors. Another objective is to analyze and understand which radiopharmaceuticals is best indicated for the detection of cell hypoxia.

Some hypotheses are also suggested:

- Cell hypoxia correlates with a higher likelihood of relapse.
- Disease-free survival at 5 years in cases of head and neck tumors and hypoxia may be related.
- There is a relationship between PET/CT tracers for hypoxia evaluation and the choice of IMRT/VMAT for treatment.
- There is a relationship between the dose deposited in radiotherapy treatment and the selected planning technique.

Results

1. PET/CT and Hypoxia in the tumor

Positron Emission Tomography (PET) allows the evaluation of molecular pathways, metabolism, proliferation, oxygen uptake, receptor and gene expression. Molecular imaging is increasingly used for dosimetric planning of volumes of interest and for investigating heterogeneity within these volumes(*2-4,18*).

The hybrid technique, PET/CT, provides to the physician tools for a more accurate diagnosis (*1,5*).

PET/CT in radiotherapy planning allows, precisely, the inclusion of macroscopic and microscopic disease and, with the administration of a specific radiopharmaceutical, it is possible to detect major and minor areas of hypoxia (*3,19*).

In healthy tissues, oxygen levels are greater than 24 mmHg, and may be up to 66 mmHg. Hypoxia is characterized by the reduced oxygen rate in cells, which is characterized by being less than 10 millimeters of mercury (mmHg), and tumors have zones of high hypoxia (*20-26*). Hypoxia can be broadly classified as acute or chronic (*6,21,26,27*). Acute or cyclic hypoxia is caused by a temporary interruption of blood flow and oxygen (*6,24,25,27*). On the other hand, chronic hypoxia results from the increased distance from the tumor to microvessels or anemia, which reduces the amount of oxygen available in the bloodstream (*22,24,26,28,29*). Chronic hypoxia is stable whereas acute hypoxia is unstable, this is, it changes over time(*21,24,25*).

The presence of hypoxia in a tumor is a poor prognostic factor, considering that is associated with greater aggressiveness, since there is a greater likelihood of metastatic spread and greater resistance to radiotherapy treatment. In radiotherapy treatment of deep tumors, X-ray radiation is used. In molecular terms, the radiation will interact with the biological tissue through the indirect effect that is superior to the direct effect in about 2/3, where the primary photon reacts with the cellular water, which in its moleculer structure contains oxygen. As a result of this interaction, free radicals are produced, damaging the DNA of the target cells. Thus, the reduced oxygen rate affects the curability of tumors, as in cases of head and neck tumors (*19,21,22,24,28,30-34*).

Authors such as Hendrickson, et al.,*(8)* Chang, et al.*(35)*, IAEA*(32)*, argue that for the same biological effect on non-hypoxic cells, the total dose of X-ray radiation in radiotherapy treatment should be up to 3 times higher in hypoxic cells.

3.Radiopharmaceuticals for the detection of tumor hypoxic cells

The radiopharmaceuticals studied for the evaluation of hypoxia in PET/CT present as radionuclides the fluorine-18 (^{18}F), copper-64 (^{64}Cu) or copper-62 (^{62}Cu). Cyclotron-produced ^{18}F has a physical half-life of 110 minutes and decays by β+ (97%) with an energy of 635keV, and an average soft-tissue range of 0.6mm(*9,20,35-37*). ^{64}Cu is a radionuclide whose physical half-life is 12.7 hours, its decay by β+ (17.8%), having a maximum energy of 0.655MeV and an average soft-tissue range of 1.4 mm(*20,38,39*). ^{62}Cu is a radionuclide with half-life 9.7 minutes and with a β^+ (97,5%) *(40,41,42,43,44).*

PET/CT allows the definition of treatment volumes such as Gross Tumor Volume (GTV) and Biological Tumor Volume (BTV). A specific hypoxia-detecting radiotracer allows the delineation of hypoxic subvolumes within the tumor volume, which is important for enhancing IMRT/VMAT treatment (*9,10,18,45*).

In 1981, the radiopharmaceutical studied for detection of hypoxic cells was ^{14}C-misonidazole. Two classes of tracers were later studied, being one of them the nitroimidazole analogs labelled with ^{18}F. These compounds act as passive diffusion nitroimidazoles into the cells. Following reduction by nitroredutases in the case of hypoxic cells, there is an accumulation of radicals within the cell. To this class belong the radiopharmaceuticals Fluorine-18-fluoromisonidazole (^{18}F-FMISO), Fluorine-18-fluoroazomycin arabinoside (^{18}F-FAZA), 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-Fluorine-18-pentafluoropropyl)-acetamide (^{18}F-EF5), Fluorine-18-fluoroerythronitro-midazole (^{18}F-FETNIM), Fluorine-18-(1-(2-1-(1H-methyl) ethoxy)-methyl-2-nitroimidazole (^{18}F-RP-170) and Fluorine-18-3-fluoro-2- (4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (^{18}F-HX4). Another class of radiopharmaceuticals is Copper-labeled diacetyl-bis, to which it belongs the Copper-64-diacetyl-bis(N^4-

methylthiosemicarbazone) (^{64}Cu-ATSM) and Copper-62-diacetyl-bis(N^4-methylthiosemicarbazone) (^{62}Cu-ATSM) (*20,23,24,29,40,42-44,46*).

For imaging acquisition, the ideal radiopharmaceutical should have adequate physical and biological half-life, in order to decay as quickly as possible so as not to increase dosimetry for the patient, but also, be slow enough to allow image formation(*47*).

For a correct visualization of the hypoxic areas of the tumor, it is important that, regardless of the cell type, there is retention in the hypoxic cells and not in oxygenated or necrotic cells. In this sense, the radiopharmaceutical should be sufficiently lipophilic to have high cellular uptake and a rapid equilibrium, or it should be hydrophilic with a faster clearance kinetics, resulting in better contrast between hypoxia and normoxia. Hypoxic variations should not interfere with radiopharmaceutical pharmacokinetics and distribution. The radiopharmaceutical activity to be administered for imaging should be relatively low, but adequate to allow imaging, the radiopharmaceutical must be reproducible, easily produced, and highly available (*24,29,38*) Moreover, an ideal radiopharmaceutical cannot demonstrate toxicity to the human organism(*47*).

The tumor/blood and tumor/muscle ratio that represents a good target/background ratios is vital in delimiting target volumes *(48)*. The authors Nehmed, et al. *(48)*, chose to use a tumor/blood ratio greater than 1.2 for volume definition.

Due to the chemical properties of radiopharmaceuticals, for each tumor location there is a more appropriate radiopharmaceutical *(29)*.

3.1. ^{18}F-FMISO

In 1986, appeared the radiopharmaceutical ^{18}F-FMISO, being currently one of the most widely used radiopharmaceuticals, mainly for the head and neck tumors (*20,23,29,35,45,49,50*). ^{18}F-FMISO is also indicated for lung and prostate tumors (*45*). Other authors also refer its utility for gliomas, renal and breast tumors (*24,29*).

^{18}F-FMISO is a lipophilic radiopharmaceutical, ranging a logP between -0.42 and -0.38. This radiopharmaceutical contains 2-nitroimidazole (*20,23,24,29,34,46,51*), and is eliminated via the hepatobiliary and gastrointestinal tract(*51*).

PET using ^{18}F-FMISO has some limitations, such as the short biological half-life, which has resulted in failure to detect hypoxia and, consequently, a higher risk of failure in the locoregional localization, low tumor/background contrast and finally low clearance of healthy tissues (*24,29,50,52*).

In addition, ^{18}F-FMISO has no specific retention and is characterized by its very slow uptake, which implies longer residence time in the patient's organism and late imaging (*23,51*).

Regarding the activity to be administered, authors such as Lee, et al. (*9*), Chang, et al.*(35)*, Hendrickson, et al.(*8*) report an administration between $3.7x10^8$ and $7.4x10^8$ becquerel (Bq).

Image acquisition, according to Lee, et al.(*9*), Chang, et al.(*35*), Hendrickson, et(*8*), should be performed 2 to 2.5 hours after radiopharmaceutical administration. However, according to Lapa, et al.*(23)*, the most acceptable time from administration to image acquisition is about 4 hours. According to the authors Choi, et al. *(52)*, Lopci, et al.(*20*), images should be acquired 2 to 4 hours after an injection, being the images acquired during 10 minutes.

The authors Lin, et al.(*53*), also suggests performing other PET/CT images to verify the efficacy and reproducibility of the radiopharmaceutical for the detection of hypoxia cells. First, a PET scan using a radiopharmaceutical such as ^{18}F-FMISO, which is sensitive to hypoxia, should be acquired. Three days after starting radiotherapy treatment, another PET/CT image with the same radiopharmaceutical should be acquired*(53)*.

3.2. ^{18}F-FETNIM

^{18}F-FETNIM radiopharmaceutical is most useful in head and neck, uterus, esophageal and lung tumors (*29,45*).

This radiopharmaceutical is considered hydrophilic, thus showing a low background signal. Its clearance is done mainly through the renal and partially hepatobiliar(*20,24,38,45*).

3.3. ^{18}F-FAZA

Authors such as Gronroos & Minn*(45)*, Lopci, et al.(*20*), Busk, et al.(*54*), Jakobsen, et al.*(55)*, Fleming, et al.(*29*), encourage the use of the radiopharmaceutical ^{18}F-FAZA, a nitroimidazole of second generation for head and neck tumors. Fleming, et al.(*29*), also refer its use in gliomas, and tumors of the lungs, uterus and colorectal.

^{18}F-FAZA is a hydrophilic radiopharmaceutical with a LogP value of 0.04 and is characterized by high contrast between normoxic and hypoxic cells due to its extremely rapid clearance in normoxic cells (*4,24,29,51,55*). Grégoire, Thorwarth, & Lee *(4)* mention the fact that some authors consider it a radiopharmaceutical of high chemical stability. Also, is useful in detecting acute hypoxia(*27*).

In the study Jakobsen, et al. *(55)*, state that ^{18}F-FAZA had a Standard Uptake Value (SUV) relatively high and demonstrated a high intratumoral contrast.

According to Carlin & Humm (*38*), image acquisition is performed 3 hours after radiopharmaceutical administration, while according to Peeters, et al.(*27*), the ideal time for image acquisition is 2 hours after radiopharmaceutical administration.

3.4.^{18}F-HX4

Radiopharmaceutical ^{18}F-HX4 is most useful in tumors such as head and neck, lung and liver *(29)*.

Contain 1,2,3-anti-triazole, being a hydrophilic molecule, having a LogP value between -0.71 and -0.67 (*24,29,51*).

The radiopharmaceutical contains 2-nitroimidazole, and has a shorter biological half-life in normoxic tissues compared to ^{18}F-FMISO (*24,27,51*).

The clearance in organs such as the intestines and liver is relatively low, occurring mostly at the renal level rapidly (*24,38,51*).

^{18}F-HX4 is one of the most sensitive radiopharmaceuticals for the detection of acute hypoxia *(27)*.

An advantage of the ^{18}F-HX4 is the relatively short time between radiopharmaceutical administration and image acquisition (*29*).

For Peeters et al.*(27)* the ideal imaging time after administration is 3 hours, demonstrating a high tumor/background ratio. The authors Hoeben, Bussink, Trooost, Oyen, & Kaandres(*18*), consider 1.5h an ideal time for obtaining images, and Fleming, et al.(*29*), refer to an ideal time for acquiring images 4 hours after administration.

3.5.^{18}F-RP-170

^{18}F-RP-170 is a useful radiopharmaceutical in tumors such as brain and lung. The usefulness for detecting hypoxia in patients with gliomas has also been demonstrated (*24,29*).

This radiopharmaceutical exhibits higher SUV values, with greater contrast between tissues (*24*).

However, as it's still a radiopharmaceutical under study, there is not much information disclosed.

3.6.^{18}F-FPIMO

Fluorine-18-labeled pimonidazole (^{18}F-FPIMO) is a 2-nitroimidazole radiopharmaceutical(*28,55*). This radiopharmaceutical uses exogenous markers such as pimonidazole(*29*).

It's considered useful for the identification of hypoxia as it has favourable chemical properties (5*5*), namely to bind to hypoxic cells in vivo, avoiding false positives (*28*).

The radiopharmaceutical ^{18}F-FPIMO, compared to ^{18}F-FAZA, has lower contrast between hypoxic and non-hypoxic cells, therefore, the SUV is also lower (54*,55*).

It was also shown that the radiopharmaceutical promotes the creation of circulating metabolites, which are metabolized or excreted by the excretion organs, such as the hepatic and renal pathways(54*,55*).

This radiopharmaceutical is still being studied and, therefore, is still not well known.

3.7.^{18}F-EF5

EF5 was first investigated in non-radioactive form. Later, as a radiopharmaceutical, it was referred to be a good indicator of tumor hypoxia regions *(56).* ^{18}F-EF5, that contain 2-nitroimidazole, binds to hypoxic cells in vivo (*28,56*).

^{18}F-EF5 easily passes through the cell membrane into cells as it is considered lipophilic (*20,24*).

The fact that this radiopharmaceutical accumulates in the same zones of hypoxia in PET images acquired at different times, and even on different days, makes ^{18}F-EF5 reproducible and viable*(17)*.

According to Komar, et al.*(57)*, for head and neck tumors, the ideal time from radiopharmaceutical administration to image acquisition is 3 hours.

3.8. ^{64}Cu-ATSM/^{62}Cu-ATSM

Another important radiopharmaceuticals for the detection of tumor hypoxia is ^{64}Cu-ATSM and ^{62}Cu-ATSM *(20,29,39,40-44,58).*

These radiopharmaceuticals are considered a neutral and low molecular weight lipophilic molecule, which means that there is a high permeability to the cell membrane and, upon its entry into the cell, is reduced to Copper (Cu) (I). Then, in the presence of hypoxic cells, it is dissociated, which causes the Cu ion to be allocated in the intracellular environment(*24,29,58*).

The radiopharmaceutical Cu-ATSM is useful for the tumors of the head and neck, lungs, kidneys, colorectal, bladder and uterus *(29)*.

The second generation ^{64}Cu-ATSM radiopharmaceutical analogs have high selectivity, providing better image quality due to their high absorption by hypoxic cells and rapid clearance of normoxic cells(*29,38,39,59,60*). The lipophilicity of this radiopharmaceutical is reduced, as is the waiting time for imaging(*29*). On the other hand, it has rapid diffusion, and the uptake occurs 10-15 minutes after administration, which correlates with the short waiting time for image acquisition (*20,24*).

However, this radiopharmaceutical has reduced renal clearance and high hepatic accumulation, which implies an increase in biological half-life and in turn dosimetry for the patient *(39,59).*

The short half-life of this radionuclide ^{62}Cu requires bigger dose of radiation but also give low dose of radiation *(40,42-44).*

Some authors use the ^{62}Cu-ATSM with copper-62-pyruvaldehyde-bis(N4-methylthiosemicarbazone), this last radiopharmaceutical have the potential to detect perfusion, they can be used for acquire images before and after the therapeutic, in the same day, due short half-time, and when they are used together, they can get the map of hypoxia more accurate. This radiopharmaceutical has a rapid clearance of the normal tissues, and the image acquisition 10-15min after injection have been used by some authors *(40,42-44).*

4. Systematic analysis of radiopharmaceuticals

An analysis of the aforementioned radiopharmaceuticals was performed, as shown in Table 2.

All the above mentioned radiopharmaceuticals, except ^{18}F-RP-170 and ^{18}F-FPIMO, are sensitive in the evaluation of hypoxia in head and neck tumors(*23,29,35,45,49,57*).

The radiopharmaceutical ^{18}F-FMISO and ^{64}Cu-ATSM is approved by the Food and Drug Administration (FDA) in the category of new drugs under investigation (41,*60,61*).

Both ^{18}F-FMISO, ^{64}Cu-ATSM and ^{18}F-EF5 are lipophilic, and their entry into the cell is facilitated by passive diffusion through the cell membrane and thus has a high retention in hypoxic cells. Radiopharmaceuticals such as ^{18}F-FETNIM, ^{18}F-FAZA and ^{18}F-HX4 are considered hydrophilic, being evident in these radiopharmaceuticals the rapid exit from normoxic cells. Both radiopharmaceutical lipophilicity and hydrophilicity are important for increased radiopharmaceutical absorption and high contrast between hypoxic and non-hypoxic cells (*4,20,23,24,29,38*). There are several authors who claim that ^{18}F-FETNIM, ^{18}F-FAZA, ^{18}F-HX4 are more hydrophilic than ^{18}F-FMISO(*20,29*).

Unlike ^{18}F-FAZA, ^{18}F-HX4 and ^{64}Cu-ATSM radiopharmaceuticals, ^{18}F-FMISO has a slower clearance in normoxic cells and therefore the distinction between hypoxic and non-hypoxic cells is not so clear (*20,27,29,38,51,52,54,55*).

When compared with the ^{18}F-FMISO radiopharmaceutical, both ^{18}F-HX4 and ^{18}F-FAZA have the particularity of detecting acute cyclic or transient hypoxia after administration as they are not influenced

by reoxygenation. The fact that these radiopharmaceuticals can identify areas of acute hypoxia helps in choosing the most appropriate therapy *(27)*.

In the Jakobsen, et al. *(55)* study, it was found that when comparing the ^{18}F-FPIMO and ^{18}F-FAZA SUV values, the latter had relatively higher SUV values, which means that it demonstrates a higher uptake in hypoxic areas, which leads to high intratumoral contrast.

Biological half-life in healthy tissues is lower for ^{18}F-HX4 and ^{18}F-FAZA, compared to ^{18}F-FMISO. Also ^{64}Cu-ATSM, ^{62}Cu-ATSM and ^{18}F-FETNIM have a short biological half-life in normoxic tissues, which implies that cell clearance in oxygenated tissues is higher (*20,27,29,40-44*).

The excretion pathway of radiopharmaceuticals is also determined by its hydrophilicity or lipophilicity. Lipophilic drugs are mostly eliminated by the hepatobiliary route, while hydrophilic drugs are mostly eliminated by the renal route. The hepatobiliary route of excretion implies a higher dosimetry for the patient as clearance is performed more slowly. On the other hand, the renal rout of excretion is performed quickly, thus implying a lower dosimetry for the patient. In the case of ^{18}F-FMISO, its excretion occurs via hepatobiliary and gastrointestinal routes (*51*). In relation to ^{18}F-FETNIM and ^{18}F-HX4 radiopharmaceuticals, clearance is mostly performed by the renal routes (*24,38,51*). ^{18}F-FPIMO clearance is hepatic and renal*(55).* ^{64}Cu-ATSM has a reduced renal clearance and marked hepatic absorption (*59*).

The ^{18}F-EF5 has a high reproducibility, which provides consistent image results from consecutively acquired PET scans(*17*).

These days it can be said that a radiopharmaceutical with all the ideal characteristics has not yet been found (*29*).

5.PET/CT in radiotherapy planning

PET images can identify areas of disease that are not easily visible in the Computed Tomography (CT) for the therapy planning, as the first imaging technique can identify molecular changes (*7,49,62*). Molecular imaging is useful for visualizing primary tumor, ganglion involvement and metastatic disease (*62,63*).

The combination of hybrid imaging for radiotherapy planning gives greater sensitivity and precision in the delimitation of the lesion, enabling a change of therapeutic approach from 10% to 30%, providing an individualized and rigorous treatment that reduces the likelihood of side effects resulting from the treatment. It also allows the construction of an accurate "map" of hypoxia zones adapted to the disease reality of each patient(*6,7,11,29,35,62,64-66*).

The main purpose of radiotherapy is to potentiate the dose at the target volume without compromising the healthy tissues. For this purpose, the delimitation of the target volume and organs at risk must be precise and accurate, and the tolerance dose at the organs at risk should not be exceeded(*7,9,11,12,62,64*). PET/CT imaging is a promising tool in treatment planning for head and neck tumors, particularly with the application of the radiotherapy treatment techniques IMRT or VMAT, as they are two non-invasive treatment techniques useful in small irregular volumes within a target volume because they can effectively distribute the radiation dose and match the volume of interest defined in PET/CT (*45,67*).

6.Advantages of the planning technique for the treatment of head and neck tumors

Head and neck tumors are sensitive to oxygen levels during radiotherapy treatment (*17*).

In the study Johansen, et al.(*16*), most relapses occurred in the locoregional lymph nodes. Some reasons for local recurrence were pointed out, such as insufficient total dose, primary tumor histological type, inaccurate therapy planning image and inadequate target volume delimitation. It may also contribute to relapses the use of highly conformal therapies by increasing the likelihood of marginal failure (*6,16,68*).

On the other hand, the PET/CT radiotherapy planning image of hypoxia, with the possibility of using different radiopharmaceuticals that allow a good intrinsic resolution and the possibility of three-dimensional tumor representation for subsequent application of the treatment techniques IMRT/VMAT, is very useful, as it allows to deposit larger amount of dose in radioresistant volumes. They are also relevant as a lower dose to the organs at risk is intended, reducing the likelihood of xerostomia and other treatment-related toxicities, increasing the Tumor Control Probability (*8,9,20,24,29,33,35,53,67*).

These planning and treatment techniques are suitable for head and neck tumors, as these cancers have proximity to risk organs and irregular contours. These limitations are overcome by the detection and evaluation of tumor hypoxia, which plays an important role in greater locoregional control by decreasing the risk of recurrences(*8,9,16,22,48,49*).

Discussion

As referred in the beginning of this work, tumor hypoxia is considered a poor prognostic factor. The presence of oxygen in a tumor, when treated with radiotherapy, enhances the occurrence of the biological effect that leads to the destruction of tumor cells. In contrast, hypoxia inhibits the occurrence of the biological effect and increases resistance to radiation therapy (*22,28,30,32*).

The low oxygenation rate of hypoxic cell regions results in the need to increase the radiation dose by 3-fold, so as to obtain similar radiotherapeutic results compared to well oxygenated areas *(8)*.

PET/CT for radiotherapy planning of head and neck tumors contributes to a better definition of regions of lower cellular oxygenation. After radioncologist planning, the treatment technique is adapted to subvolume irradiation to counteract resistance to therapy (*4,29,66*). Molecular imaging leads to a change in the therapeutic approach as compared to other image planning techniques and thus allows to increase the therapeutic efficacy as well as contributes to a decrease of intraobserver and interobserver variability (*7,62,63*).

Radiopharmaceuticals for the detection of tumor hypoxia are ^{18}F-FMISO, ^{18}F-FETNIM, ^{18}F-FAZA, ^{18}F-HX4, ^{18}F-RP-170, ^{18}F-FPIMO, ^{18}F-EF5, ^{62}Cu-ATSM and ^{64}Cu-ATSM as they are sensitive to hypoxia (*17,29,33,35,40,42,43,51,55,56,58,59*).

Still, none of the radiopharmaceuticals currently exhibits all the ideal properties, which may be a limitation. These radiopharmaceuticals are still under investigation *(29)*. However according to Kelada & Carlson *(19)*, Komar, et al. *(57)*, ^{18}F-EF5 is a promising radiopharmaceutical, but needs further clinical studies. On the other hand, ^{18}F-FAZA due to its chemical characteristics such as its high hydrophilicity, high

affinity for hypoxia, high tumor/background contrast and its ability to detect acute hypoxia is also promising.

Through PET/CT, the accuracy in target volume planning and delimitation of the organs at risk, is increased. With IMRT/VMAT treatment techniques there is a highly conformal dose in the volume to be treated, in order to decrease the dose to organs at risk with high Tumor Control Probability (*4,6,35,68*).

Conclusion

The validity of using PET/CT for radiotherapy planning considering tumor hypoxia and the subsequent treatment with IMRT/VMAT remains under study, as some responses are still needed, including the importance and real clinical efficacy of this planning technique in the follow-up of cancer patients*(28)*. In future studies, it is also necessary to establish a PET/CT imaging protocol for the evaluation of areas of acute and chronic hypoxia and to clarify the side effects with hypoxia-directed radiotherapy treatment.

Disclosure

No overlap with other materials already published or submitted for publication, and there is no conflict of interest of any kind. No financial support.

References

1.Munshi N. Imaging Evolution: Hybrid PET/CT Scans. *Imaging Techonology News.* https://www.itnonline.com/article/imaging-evolution-hybrid-petct-scans. Accessed 12/9/2020.

2.Czernin J, Schelbert H, PET/CT Imaging: Facts, Opinions, Hopes, and Questions. *J Nucl Med.* 2004;45:1-3.

3.EANM. PET/CT Radiotherapy Planning: A Technologist Guide. Austria: *SIEMENS*.

4.Grégoire V, Thorwarth D, Lee JA. Molecular Imaging-Guided Radiotherapy for the Treatment of Head-and-Neck Squamous Cell Carcinoma: Does it Fulfill the Promises? *Semin Radiat Oncol*. 2018 ;28(1):35-45

5.Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. *Radiographics.* 2004;24:523-543.

6.Vanderstraeten B, Duthoy W, De Gersem W, De Neve W, Thierens H. [18F]fluoro-deoxy-glucose positron emission tomography [18F]FDG-PET voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. *Radiother Oncol.* 2006;79:249-258.

7.Gupta T, Beriwal S. PET/CT-guided radiation therapy planning: from present to the future. *Indian J Cancer.* 2010;47:126-133.

8.Hendrickson K, Phillips M, Smith W, Peterson L, Krohn K, Rajendran J. Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance. *Radiother Oncol.* 2011;101:369-375.

9.Lee NY, Mechalakos JG, Nehmeh S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys.* 2008;70:2-13.

10. Welsh L, Panek R, McQuaid D, et al. Prospective, longitudinal, multi-modal functional imaging for radical chemo-IMRT treatment of locally advanced head and neck cancer: the INSIGHT study. *Radiat Oncol.* 2015;10:112.

11. Delikgoz Soykut E, Ozsahin EM, Yukselen Guney Y, et al. The use of PET/CT in radiotherapy planning: contribution of deformable registration. *Front Oncol.* 2013;3:33.

12. Ceylan Y, Omur O, Hatipoglu F. Contribution of (18)F-FDG PET/CT to Staging of Head and Neck Malignancies. *Mol Imaging Radionucl Ther.* 2018;27:19-24.

13.SNMMI.Head and Neck Cancers. http://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=947. Accessed 13/12/2018, 2018.

14.RORENO.Registo Oncológico Nacional 2010. http://www.roreno.com.pt/pt/publicacoes/publicacoes-nacionais.html. Accessed 15/5/2018, 2018.

15. Estevao R, Santos T, Ferreira A, Machado A, Fernandes J, Monteiro E. Epidemiological and Demographic Characteristics of Patients with Head and Neck Tumours in the Northern Portugal: Impact on Survival. *Acta Med Port.* 2016;29:597-604.

16. Johansen S, Norman MH, Dale E, et al. Patterns of local-regional recurrence after conformal and intensity-modulated radiotherapy for head and neck cancer. *Radiat Oncol.* 2017;12:87.

17. Silvoniemi A, Suilamo S, Laitinen T, et al. Repeatability of tumour hypoxia imaging using [(18)F]EF5 PET/CT in head and neck cancer. *Eur J Nucl Med Mol Imaging.* 2018;45:161-169.

18. Hoeben BA, Bussink J, Troost EG, Oyen WJ, Kaanders JH. Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer. *Acta Oncol.* 2013;52:1257-1271.

19. Kelada OJ, Carlson DJ. Molecular imaging of tumor hypoxia with positron emission tomography. *Radiat Res.* 2014;181:335-349.

20. Lopci E, Grassi I, Chiti A, et al. PET radiopharmaceuticals for imaging of tumor hypoxia: a review of the evidence. *Am J Nucl Med Mol Imaging.* 2014;4:365-384.

21. Matsumoto S, Yasui H, Mitchell JB, Krishna MC. Imaging cycling tumor hypoxia. *Cancer Res.* 2010;70:10019-10023.

22. Walsh JC, Lebedev A, Aten E, Madsen K, Marciano L, Kolb HC. The clinical importance of assessing tumor hypoxia: relationship of tumor hypoxia to prognosis and therapeutic opportunities. *Antioxid Redox Signal.* 2014;21:1516-1554.

23. Lapa P, Jacobetty M, Teixeira T, et al. Avaliação de hipóxia tumoral por PET/CT com Fluoromisonidazol (18F) no planeamento em radioterapia. Experiência inicial. *ARP.* 2015;XXVII:59-65.

24. Challapalli A, Carroll L, Aboagye EO. Molecular mechanisms of hypoxia in cancer. *Clin Transl Imaging.* 2017;5:225-253.

25. Eales KL, Hollinshead KE, Tennant DA. Hypoxia and metabolic adaptation of cancer cells. *Oncogenesis.* 2016;5:e190.

26. Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckl).* 2015;3:83-92.

27. Peeters SGJA, Zegers CML, Lieuwes NG, et al. A Comparative Study of the Hypoxia PET Tracers [F-18]HX4, [F-18]FAZA, and [F-18]FMISO in a Preclinical Tumor Model. *Int J Radiat Oncol Biol Phys.* 2015;91:351-359.

28. Rademakers SE, Span PN, Kaanders JH, Sweep FC, van der Kogel AJ, Bussink J. Molecular aspects of tumour hypoxia. *Mol Oncol*. 2008;2:41-53.

29. Fleming IN, Manavaki R, Blower PJ, et al. Imaging tumour hypoxia with positron emission tomography. *Br J Cancer*. 2015;112:238-250.

30. Okamoto S, Shiga T, Yasuda K, et al. High reproducibility of tumor hypoxia evaluated by 18F-fluoromisonidazole PET for head and neck cancer. *J Nucl Med.* 2013;54:201-207.

31. Cardenas-Navia LI, Mace D, Richardson RA, Wilson DF, Shan S, Dewhirst MW. The pervasive presence of fluctuating oxygenation in tumors. Cancer Res. 2008;68:5812-5819.

32.IAEA. Radiation Oncology Physics: A Handbook for Teachers and Students. VIENNA: *IAEA*; 2005.

33. Thorwarth D, Welz S, Mönnich D, et al. Prospective evaluation of a tumor control probability model based on dynamic 18F-FMISO PET for head and neck cancer radiotherapy. *J Nucl Med.* 2019;60(12):1698-1704.

34. Betts HM, O'Connor RA, Christian JA, et al. Hypoxia imaging with [18F]HX4 PET in squamous cell head and neck cancers: a pilot study for integration into treatment planning. *Nucl Med Commun.* 2019;40(1):73-78.

35.Chang JH, Wada M, Anderson NJ, et al. Hypoxia-targeted radiotherapy dose painting for head and neck cancer using 18F-FMISO PET: a biological modeling study. *Acta Oncol.* 2013;52:1723-1729.

36. Jacobson O, Kiesewetter DO, Chen X. Fluorine-18 radiochemistry, labeling strategies and synthetic routes. *Bioconjug Chem.* 2015;26:1-18.

37. Salem A, Asselin MC, Reymen B, et al. Targeting hypoxia to improve non-small cell lung cancer outcome. *J Natl Cancer Inst.* 2018;110.

38. Carlin S, Humm JL. PET of hypoxia: current and future perspectives. *J Nucl Med.* 2012;53:1171-1174.

39. Anderson CJ, Ferdani R. Copper-64 radiopharmaceuticals for PET imaging of cancer: advances in preclinical and clinical research. *Cancer Biother Radiopharm*. 2009;24:379-393.

40. Wong TZ, Lacy JL, Petry NA, et al. PET of hypoxia and perfusion with 62Cu-ATSM and 62Cu-PTSM using a 62Zn/62Cu generator. *AJR Am J Roentgenol*. 2008;190(2):427-432.

41. Anderson CJ, Ferdani R. Copper-64 radiopharmaceuticals for PET imaging of cancer: advances in preclinical and clinical research. *Cancer Biother Radiopharm*. 2009;24(4):379-393.

42. Fujibayashi Y, Taniuchi H, Yonekura Y, Ohtani H, Konishi J, Yokoyama A. Copper-62-ATSM: a new hypoxia imaging agent with high membrane permeability and low redox potential. *J Nucl Med*. 1997;38(7):1155-1160.

43. Zhang T, Das SK, Fels DR, et al. PET with 62Cu-ATSM and 62Cu-PTSM is a useful imaging tool for hypoxia and perfusion in pulmonary lesions. *AJR Am J Roentgenol*. 2013;201(5):W698-W706.

44. Lapi SE, Lewis JS, Dehdashti F. Evaluation of hypoxia with copper-labeled diacetyl-bis(N-methylthiosemicarbazone). *Semin Nucl Med*. 2015;45(2):177-185.

45. Gronroos T, Minn H. Imaging of tumour hypoxia using PET and 18F-labelled tracers: biology meets technology. *Eur J Nucl Med Mol Imaging.* 2007;34:1563-1565.

46. Yu W, Qiao F, Su X, et al. 18F-HX4/18F-FMISO-based micro PET for imaging of tumor hypoxia and radiotherapy-associated changes in mice. *Biomed Pharmacother*. 2019;119:109454.

47. Duncan D. 15. Use of radionuclides in imaging and therapy. In: Cherry PDA, ed. *Practical Radiotherapy-Physics and Equipment*. second ed. United Kingdom: Wiler-Blackwell; 2009.

48. Nehmeh SA, Lee NY, Schroder H, et al. Reproducibility of intratumor distribution of (18)F-fluoromisonidazole in head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:235-242.

49. Ferrer Albiach C, Conde Moreno A, Rodriguez Cordon M, et al. Contribution of hypoxia-measuring molecular imaging techniques to radiotherapy planning and treatment. *Clin Transl Oncol.* 2010;12:22-26.

50. Grkovski M, Schoder H, Lee NY, et al. Multiparametric Imaging of tumor hypoxia and perfusion with (18)F-fluoromisonidazole dynamic PET in head and neck cancer. *J Nucl Med.* 2017;58:1072-1080.

51. Dubois LJ, Lieuwes NG, Janssen MHM, et al. Preclinical evaluation and validation of [F-18]HX4, a promising hypoxia marker for PET imaging. *Proc Natl Acad Sci USA.* 2011;108:14620-14625.

52. Choi W, Lee SW, Park SH, et al. Planning study for available dose of hypoxic tumor volume using fluorine-18-labeled fluoromisonidazole positron emission tomography for treatment of the head and neck cancer. *Radiother Oncol.* 2010;97:176-182.

53. Lin Z, Mechalakos J, Nehmeh S, et al. The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2008;70:1219-1228.

54. Busk M, Mortensen LS, Nordsmark M, et al. PET hypoxia imaging with FAZA: reproducibility at baseline and during fractionated radiotherapy in tumour-bearing mice. *Eur J Nucl Med Mol Imaging.* 2013;40:186-197.

55. Jakobsen S, Busk M, Horsman MR, et al. PET imaging of tumor hypoxia using 18F-labeled pimonidazole. *Acta Oncol.* 2013;52:1300-1307.

56. Chitneni SK, Bida GT, Yuan H, et al. 18F-EF5 PET imaging as an early response biomarker for the hypoxia-activated prodrug SN30000 combined with radiation treatment in a non-small cell lung cancer xenograft model. *J Nucl Med.* 2013;54:1339-1346.

57. Komar G, Seppanen M, Eskola O, et al. 18F-EF5: a new PET tracer for imaging hypoxia in head and neck cancer. *J Nucl Med.* 2008;49:1944-1951.

58. Hueting R, Kersemans V, Cornelissen B, et al. A comparison of the behavior of (64)Cu-acetate and (64)Cu-ATSM in vitro and in vivo. *J Nucl Med.* 2014;55:128-134.

59. Carlin S, Zhang H, Reese M, Ramos NN, Chen Q, Ricketts SA. A comparison of the imaging characteristics and microregional distribution of 4 hypoxia PET tracers. *J Nucl Med.* 2014;55:515-521.

60.NIH. FMISO Documentation *CIP-Cancer Imaging Program* https://imaging.cancer.gov/programs_resources/cancer-tracer-synthesis-resources/FMISO_documentation.htm. Accessed 22/9/2020, 2018.

61.NIH. IND Regulatory & Manufacturing Resources. *Cancer Imaging Program* https://imaging.cancer.gov/programs_resources/IND_regulatory_manufacturing.htm. Accessed 22/7/2019, 2018.

62. Sattler B, Lee JA, Lonsdale M, Coche E. PET/CT (and CT) instrumentation, image reconstruction and data transfer for radiotherapy planning. *Radiother Oncol.* 2010;96:288-297.

63. Sciences NML. PET/CT planning beneficial for head and neck cancer patients. http://www.news-medical.net/news/2008/03/06/35993.aspx# Accessed 27/7/2020, 2008.

64. Gregoire V, Chiti A. PET in radiotherapy planning: particularly exquisite test or pending and experimental tool? *Radiother Oncol.* 2010;96:275-276.

65.IAEA. *The Role of PET/CT in Radiation Treatment Planning for Cancer Patient Treatment*: *IAEA*; 2008.

66. Parodi K. Vision 20/20: Positron emission tomography in radiation therapy planning, delivery, and monitoring. *Med Phys.* 2015;42:7153-7168.

67.83ICRU. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Contents. *J ICRU.* 2010;10:NP-NP.

68. Chakraborty S, Patil VM, Babu S, Muttath G, Thiagarajan SK. Locoregional recurrences after post-operative volumetric modulated arc radiotherapy (VMAT) in oral cavity cancers in a resource constrained setting: experience and lessons learned. *Br J Radiol.* 2015;88:20140795.

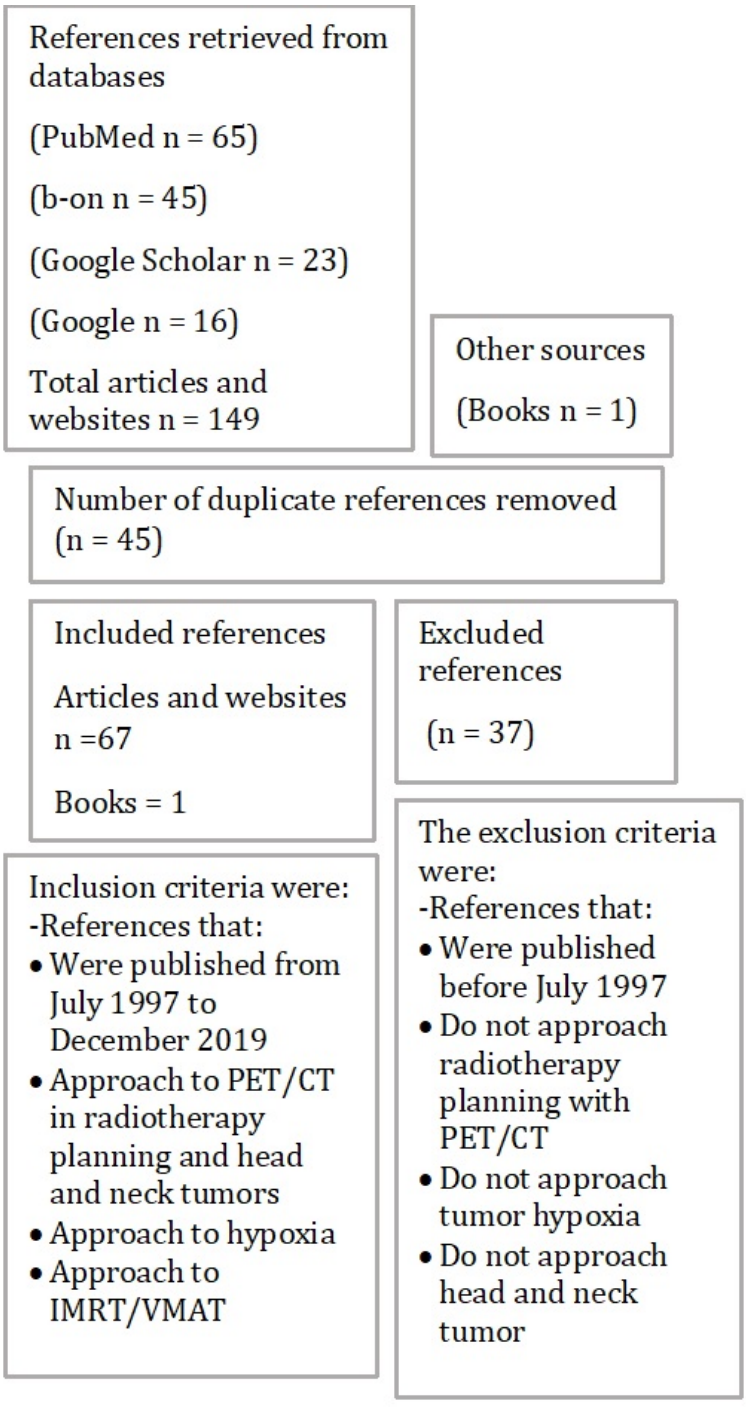

Figure 1. Flowchart of inclusion/exclusion of bibliographic references

TABLE 1-Incidence and mortality rate of Head and Neck Tumors. Adapted from RORENO (*14*)

Head and Neck Tumors	Incidence rate per 100.000	Mortality rate per 100.000
Lip	2	0,1
Tongue	3	1,3
Oral Cavity	3,1	1,3
Salivary Glands	1	0,5
Amygdala	1,3	0,4
Oropharynx-others	1,2	1
Nasopharynx	0,9	0,5
Hipopharynx	2,1	0,9
Pharynx- others	0,4	0,6
Larynx	5,9	3,7

Table 2- Systematic analysis of the radiopharmaceuticals used in PET/CT to evaluate hypoxic cells (Own authorship)

	Head and Neck Tumors	Lipophilic/ Hydrophilic	LogP Values	Radiopharma-ceuticals sensitive to acute hypoxia detection	Image acquisition time after administration	SUV	Non-hypoxic cells clearance velocity	Reproducibility of radiopharmaceu-ticals	Excretion route
^{18}F-FMISO	✓(*23,29,35,45,49*)	**Lipophilic** (*23,24,29*)	**Between -0,42 and -0,38**(51)	**Not mentioned**	**Between 2 and 4h**(*9,20,23,35,52*)	**Not mentioned**	↓(*52*)	**Not mentioned**	**Hepatobiliary and gastrointestinal tract**(*51*)
^{18}F-FETNIM	✓(*29,45*)	**Hydrophilic** (*24,38*)	**Not mentioned**	**Not mentioned**	**Not mentioned**	**Not mentioned**	↑(*20*)	**Not mentioned**	**Rapid renal clearance and low hepatic clearence** (*24,38*)
^{18}F-FAZA	✓(*29,45*)	**Hydrophilic** (*24,29*)	**0,04**(*51*)	✓(*27*)	**Between 2 and 3h**(18, *27*)	↑(*55*)	↑(*4,29,55*)	**Not mentioned**	**Not mentioned**
^{18}F-HX4	✓(*29*)	**Hydrophilic** (*24,29*)	**Between -0,71 and -0,67**(*51*)	✓(*27*)	**Between 1,5 and 4h** (*18,27*)	**Not mentioned**	↑(*51*)	**Not mentioned**	**Intestinal, hepatic low and mostly renal** (*24,38,51*)
^{18}F-RP-170	**Not mentioned**	**Not mentioned**	**Not mentioned**	**Not mentioned**	**Not mentioned**	↑(*24*)	**Not mentioned**	**Not mentioned**	**Not mentioned**
^{18}F-FPIMO	**Not mentioned**	**Not mentioned**	**Not mentioned**	**Not mentioned**	**Not mentioned**	↓(*55*)	**Not mentioned**	**Not mentioned**	**Hepatic and renal tract**(*55*)
^{18}F-EF5	✓(29,57)	**Lipophilic** (*20,24*)	**Not mentioned**	**Not mentioned**	**3h**(*57*)	**Not mentioned**	**Not mentioned**	↑(*17*)	**Not mentioned**
^{62}Cu-ATSM	✓(*29*)	**Neutral Lipophilic** *(42,44)*	**Not mentioned**	**Not mentioned**	**10-15 min***(40, 42)*	**Not mentioned**	↑*(42-44)*	**Not mentioned**	**Not mentioned**
^{64}Cu-ATSM	✓(*29*)	**Neutral Lipophilic** (20,*24*)	**Not mentioned**	**Not mentioned**	**10-15 min***(20,24)*	**Not mentioned**	↑(*29,38*)	**Not mentioned**	**Reduced renal clearance and high liver accumulation**(*59*)