^{18}F-FDG and Non-FDG PET Radiopharmaceuticals

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Contents

5.1 Introduction

Positron emission tomography/computed tomography (PET/CT) is one of the key imaging techniques in oncology. Hybrid PET/CT provides both structural and metabolic information and in general improves sensitivity, specificity and reporter confidence.

Fluorine-18 (^{18}F) is the most commonly used PET-emitting radionuclide label in clinical practice. It is produced using a cyclotron and has a physical half-life of 110 min. The most widely used tracer at present is the glucose analogue, 2-fluoro-2-deoxyglucose (FDG) (Table 5.1).

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5.2 PET Radiopharmaceuticals

5.2.1 ^{18}F-FDG

^{18}F-FDG has a role in localising, characterising, staging and monitoring treatment response and evaluation of recurrent disease in a variety of cancer types. However, increased FDG uptake is not specific to cancer cells. FDG accumulates in cells, in proportion to glucose utilisation [1–5]. In general, increased glucose uptake is a characteristic of most cancers and is in part mediated by overexpression of the GLUT-1 glucose transporter and increased hexokinase activity [1–5]. The net result is an increased accumulation of FDG within tumour cells at a rate greater than in normal tissue. Active inflammatory changes can also result in increased FDG uptake, due to increased glucose utilisation by activated granulocytes and mononuclear cells [1–5] (Tables 5.1–5.3). The principal route of excretion of FDG from the bloodstream is via the urinary tract. The biodistribution of ^{18}F-FDG varies on several factors such as (a) fasting state, (b) medications, (c) duration of the uptake period post tracer injection, (d) variant metabolism, (e) incidental pathology, etc.

Table 5.1 Oncology PET radiopharmaceuticals [1–11]

Class	Radiopharmaceutical	Clinical application
Oncology: ^{18}F	Fludeoxyglucose (FDG)	Glucose metabolism
	Fluoride	Bone metabolism
	Fluoro-L-thymidine (FLT)	DNA synthesis
	Fluoromethylcholine (FCH)	Phospholipid synthesis
	Fluoroethylcholine (FEC)	Phospholipid synthesis
	Fluoroethyltyrosine (FET)	Protein synthesis
	Fluoromisonidazole (FMISO)	Hypoxia
	Fluoroazomycin arabinoside (FAZA)	Hypoxia
	Fluoroerythronitroimidazole (FETNIM)	Hypoxia
	Fluciclatide	Angiogenesis
	F-Galacto-RGD	Angiogenesis
	Fluciclovine (FACBC)	Amino acid transport
	ICMT11	Apoptosis
Oncology: ^{11}C	Acetate	Membrane synthesis
	Choline	Phospholipid synthesis
	Methionine	Protein synthesis
Oncology: ^{68}Ga	DOTATOC	Somatostatin receptor
	DOTATATE	Somatostatin receptor
	HA-DOTATATE	Somatostatin receptor
	DOTANOC	Somatostatin receptor
	Somatoscan	Somatostatin receptor
	PSMA	Prostate-specific membrane antigen
	NOTA-RGD	Angiogenesis
Oncology: ^{124}I	Iodide	Sodium iodide symporter
	MIBG	Neuronal activity

Table 5.2 Properties of positron-emitting radionuclides used in clinical practice

Radionuclide	Half-life	Positron energy (max, MeV)	Other emissions	Means of production
Carbon-11	20 min	0.96	–	Cyclotron
Nitrogen-13	10 min	1.20	–	Cyclotron
Oxygen-15	2 min	1.74	–	Cyclotron
Fluorine-18	110 min	0.63	–	Cyclotron
Copper-62	10 min	2.93	–	Generator
Copper-64	13 h	0.65	Beta, gamma	Cyclotron
Gallium-68	68 min	1.83	–	Generator
Rubidium-82	76 s	3.15	–	Generator
Zirconium-89	79 h	0.40	Gamma	Cyclotron
Iodine-124	4.2 days	1.50	Gamma	Cyclotron

Table 5.3 Common radiopharmaceuticals and their mechanism of uptake [11]

Radiotracer	Mechanism of uptake
^{18}F-Fluorodeoxyglucose (FDG)	Uptake by GLUT-1 transporter followed by phosphorylation by hexokinase
Sodium ^{18}F-fluoride (NaF)	Incorporated within hydroxyapatite in proportion to bone metabolism
^{68}Ga-labelled peptides	Bind to peptide receptor, most commonly somatostatin receptor
^{18}F-Choline (FCH) ^{11}C-Choline	Incorporation into phosphatidylcholine as part of cell wall synthesis
^{11}C-Methionine	Amino acid transport
^{18}F-Fluorothymidine (FLT) ^{11}C-Thymidine	Phosphorylated by thymidine kinase in proliferating cells, FLT not incorporated into DNA
^{82}Rb-Chloride	Transported into myocardial cells by sodium-potassium ATPase in proportion to regional myocardial perfusion

5.2.2 Non-FDG Radiopharmaceuticals

In addition to ^{18}F-FDG, there are several cyclotron- and generator-based radiolabelled molecules used in clinical PET/CT imaging. Sodium fluoride (^{18}F-NaF), ^{68}Ga-labelled peptides, ^{18}F-choline, ^{11}C-choline, etc. each have clinical applications and are discussed in detail in this pocket book series titled 'PET Radiotracers'. While FDG is the workhorse of oncological PET imaging, it is non-specific as it monitors the ubiquitous process of glucose metabolism. Alternative tracers tend to be more specific in their targeting and application. Some attempt to probe the hallmarks of cancer, such as uncontrolled proliferation, angiogenesis, evasion of apoptosis and tissue invasion. Tumour microenvironment, such as hypoxia, has also been probed. However, the tracers which have come into wider use tend to be those which monitor specific features such as membrane synthesis incorporating choline, prostate-specific membrane antigen (PSMA) expression and somatostatin receptor expression.

Conclusion

It is likely that the range of positron-emitting radiopharmaceuticals in routine clinical use will continue to expand in the coming years.

Key Points

- Fluorine-18 (^{18}F) is the most commonly used PET-emitting radionuclide label in clinical practice.
- Fluorine-18 (^{18}F) is produced using a cyclotron and has a physical half-life of 110 min.
- Most widely used tracer at present is the glucose analogue, 2-fluoro-2-deoxyglucose (FDG). FDG is the workhorse of oncological PET imaging.
- FDG is actively transported into the cell mediated by a group of structurally related glucose transport proteins (GLUT).
- Increased FDG uptake is not specific to cancer cells and often will accumulate in areas with increased metabolism and glycolysis.
- The principal route of excretion of FDG from the bloodstream is via the urinary tract.
- Non-FDG tracers include sodium fluoride (^{18}F-NaF), ^{68}Ga-labelled peptides, ^{18}F-choline and ^{11}C-choline.

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