Nouveaux isotopes pour le diagnostic et traitement du cancer du pancréas, une collaboration avec le CERN

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NOUVEAUX ISOTOPES POUR LE DIAGNOSTIC ET TRAITEMENT DU CANCER DU PANCRÉAS, UNE COLLABORATION AVEC LE CERN

Thèse
présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine
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Thèse **nº 10981**

Genève, Décembre 2019

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1. Abstract

1.1 Résumé (français)

L'utilisation de la radioactivité dans la médecine a été développée depuis plus d'un siècle. La découverte des radioisotopes et de leurs interactions avec la matière a permis l'émergence de nouvelles modalités diagnostiques et thérapeutiques.

L'infrastructure CERN-MEDICIS récemment inaugurée au Centre Européen pour la Recherche Nucléaire (CERN), met à disposition une quantité variée de radioisotopes de grand intérêt pour le diagnostic et la thérapie en oncologie notamment.

Notre objectif est d'attirer l'attention sur les progrès réalisés en médecine nucléaire en collaboration avec le CERN et les futures applications potentielles, en particulier pour le traitement de tumeurs au pronostic réservé tel que l'adénocarcinome du pancréas, à travers une revue extensive de la littérature.

97 sur 227 articles, publiés entre 1984 et 2019, ont été sélectionnés en fonction de leur pertinence. Plusieurs entretiens ont été organisés avec un groupe multi-discipilinaire composé de physicien, ingénieur biologiste, chimiste, oncologue et chirurgien participant activement au projet CERN-MEDICIS.

En conclusion, de nouvelles modalités diagnostiques et thérapeutiques émergent pour le traitement de l'adénocarcinome du pancréas. La radiothérapie vectorisée interne ou la brachythérapie pourraient être combinées aux thérapies actuelles pour améliorer la qualité de vie et la survie de ces patients. La plupart des études sont encore au stade pré-clinique mais ouvrent des voies prometteuses pour les patients au pronostic réservé.

1.2 Summary (english)

The use of radioactivity in medicine has been developed over a century. The discovery of radioisotopes and their interactions with living cells and tissue has led to the emergence of new diagnostic and therapeutic modalities.

The CERN-MEDICIS infrastructure, recently inaugurated at the European Centre for Nuclear Research (CERN), provides a wide range of radioisotopes of interest for diagnosis and treatment in oncology.

Our objective is to draw attention to the progress made in nuclear medicine in collaboration with CERN and potential future applications, in particular for the treatment of aggressive tumors such as pancreatic adenocarcinoma, through an extensive review of literature.

97 out of 227 articles, published between 1984 and 2019, were selected based on relevancy. Meetings were held with a multi-disciplinary team, including a physicist, a biological engineer, a chemist, an oncologist and a surgeon, actively involved in the CERN-MEDICIS project.

In conclusion, new diagnostic and therapeutic modalities are emerging for the treatment of pancreatic adenocarcinoma. Unsealed source therapy or brachytherapy could be combined with existing therapies to improve the quality of life and survival of these patients. Many studies are still in the pre-clinical stage but open new paths for patients with poor prognosis.

2. Introduction (Français)

2.1 Histoire de la médecine nucléaire

La découverte des rayons X par Wihelm Conrad Röntgen en 1895, alors qu'il travaillait avec des tubes cathodiques, fut la première étape dans l'histoire de l'utilisation des rayons nucléaires en médecine.
Ce progrès fut suivi en 1896 par les résultats d'Henri Becquerel qui, en travaillant avec des sels d'uranium, découvrit la radioactivité naturelle (aussi appelée "spontanée"), à savoir le fait que le rayonnement provient de l'uranium lui-même, sans besoin d'excitation par une source énergétique externe. Sa doctorante, Marie Curie, découvrit plus tard d'autres éléments radioactifs : le thorium, polonium et radium. Le radium rapidement suscita un intérêt général pour le traitement de diverses maladies et souleva des préoccupations en matière de santé publique.
Ernest Rutherford étudia les propriétés des désintégrations radioactives et les nomma alpha, bêta et gamma en 1899, les classant selon leur capacité à pénétrer la matière.
Plus tard, il fut découvert que les rayons X et le rayonnement gamma sont de la même nature : ce sont des rayonnements électromagnétiques, qui au niveau quantique peuvent être décrits par l'émission de particules neutres de masse nulle, les photons [1].

Ce fut George de Hevesy qui développa l'idée qu'un atome stable dans le corps pourrait être remplacé par la forme radioactive du même élément sous la forme d'un traceur. Il développa en 1935 le premier traceur radioactif en utilisant le ^{32}P chez l'animal, pour lequel il lui fut décerné le prix Nobel de chimie en 1943 [2].
En 1941, Saul Hertz découvrit l'utilisation de l'iode radioactif pour le traitement de la maladie thyroïdienne. Aujourd'hui, il est encore couramment utilisé sous diverses formes.
Le ^{99}Tc est également très couramment utilisé. Il a été isolé pour la première fois en 1938 et introduit comme radiotraceur médical dans les années 1950.

Au cours des cent dernières années, divers nouveaux éléments radioactifs ont été découverts et sont actuellement utilisés dans le domaine médical. Les progrès de la médecine nucléaire n'ont été possibles que grâce aux connaissances acquises en physique de la structure nucléaire, des désintégrations radioactives et de l'interaction du rayonnement avec la matière. Ces sujets seront traités dans la section suivante.

2.2 Médecine nucléaire : connaissances de base et définitions

a) Définition des isotopes, des rayonnements alpha, bêta et gamma

Un noyau est caractérisé par le nombre de protons et de neutrons. Les noyaux sont représentés sous la forme $^{A}_{Z}X$, X étant le symbole chimique de l'élément. La lettre A correspond au nombre de masse atomique et est égal à la somme du nombre de protons, Z, et des neutrons, N. Les noyaux avec le même nombre atomique Z et un nombre différent de neutrons sont nommés isotopes. Chaque numéro atomique Z identifie un élément spécifique, mais un atome d'un élément donné peut exister dans la nature ou être produit artificiellement avec un nombre différent de neutrons N, résultant en une large gamme d'isotopes.

Certains isotopes sont instables, ils se désintègrent en émettant des rayonnements et sont donc appelés radioactifs ou radio-isotopes, alors que d'autres sont nommés isotopes stables. L'émission radioactive peut être spontanée ou induite par l'exposition à un rayonnement spécifique. Un noyau parent émettra à travers sa désintégration en un noyau fille différentes particules : alpha, bêta ou gamma.

Le rayonnement alpha correspond à l'émission d'une particule alpha, qui est identique au noyau d'hélium ($^{4}He^{2+}$), composé de 2 protons et 2 neutrons. La charge électrique d'une particule alpha est donc deux fois supérieure à celle d'un proton. Après l'émission d'une particule alpha par un atome, son nombre de masse est réduit de quatre et son numéro atomique est réduit de deux. La désintégration radioactive alpha est représentée par l'expression suivante :

$$^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y + {}^{4}_{2}He$$

Le rayonnement bêta est classé en différents processus : la désintégration bêta+, la désintégration bêta- et la capture d'électrons. La désintégration bêta+ est caractérisée par l'émission d'un positron, qui est un antiélectron (particule ayant les mêmes caractéristiques qu'un électron mais avec une charge électrique opposée) et un neutrino, comme représenté ci-dessous :

$$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + ß^{+} + \text{neutrino}$$

La désintégration bêta- consiste en l'émission d'un électron et d'un antineutrino :

$^{A}_{Z}X \rightarrow {}^{A}_{z+1}Y + ß^{-} + \text{antineutrino}$

Enfin, dans le noyau atomique, le processus de capture d'électrons peut aussi se produire. Il est représenté sous la forme suivante :

$^{A}_{Z}X + e^{-} \rightarrow {}^{A}_{Z-1}Y + \text{neutrino}$

Le rayonnement gamma est l'émission d'un photon par un noyau excité selon l'expression suivante :

$^{A}_{Z}X^{*} \rightarrow {}^{A}_{Z}X + \text{photon}$

où X* represente la forme excitée du noyau X.

Un autre processus radioactif d'intérêt est la conversion interne, un processus électromagnétique au cours duquel l'interaction du champ électromagnétique d'un noyau excité avec un électron orbital entraîne l'éjection de l'électron de l'atome avec un spectre énergétique discret.

$^{A}_{Z}X^{*} \rightarrow {}^{A}_{Z}X + \text{electron}$

Après ce processus, le trou laissé dans la couche d'électrons de l'atome est ensuite rempli par d'autres électrons qui descendent à ce niveau d'énergie inférieur. Au cours de ce processus : (i) des photons dans le domaine des rayons X, (ii) des électrons appelés électrons Auger, ou (iii) les deux, sont ensuite émis.

Une forme de désintégration radioactive est le processus de fission spontanée dans lequel un un noyau lourd se divise, sans apport d'énergie extérieur, en au moins deux noyaux plus légers. Ces noyaux sont instables et donnent lieu à une chaine de désintégrations radioactives. Le processus de fission peut être induit aussi par une interaction nucléaire d'un neutron avec un noyau.

Un radio-isotope se transforme en un noyau fille stable ou instable à travers les différents types de désintégrations décrits auparavant en un temps caractéristique, correspondant à la "demi-vie". Un composé radioactif est caractérisé par le nombre d'émissions par unité de temps, que l'on nomme "activité". La demi-vie est le temps nécessaire pour que l'activité d'une quantité donnée d'une substance radioactive se désintègre à la moitié de sa valeur initiale.

Le noyau fille, s'il est instable, se désintégrera à son tour et un processus en cascade se déroulera jusqu'à ce que, finalement, des éléments stables soient produits.

b) Interaction des particules avec la matière

Lorsque les particules finales d'une désintégration radioactive traversent la matière, différents mécanismes d'interaction entre les particules et les atomes de la matière ont lieu. Après l'interaction, une particule peut ralentir, changer de direction ou être absorbée. Si le bloc de matière est suffisamment épais, une longueur de pénétration peut être définie pour chaque particule chargée en fonction de la valeur de sa charge électrique, de son énergie initiale et des caractéristiques du matériau traversé.
Les particules lourdes chargées électriquement, en particulier les particules alpha ou les protons de faible énergie, interagissent principalement par ionisation directe et excitation du noyau. L'énergie déposée par la particule par unité de longueur (le transfert d'énergie linéaire) dépend du carré de sa charge électrique, il est donc quatre fois supérieur pour une particule alpha que pour un proton de la même vitesse. Dans ce processus, lorsque l'énergie totale de la particule est environ trois fois inférieure à son énergie au repos, le transfert d'énergie linéaire augmente fortement lorsque la vitesse des particules diminue. Par conséquent, ce processus est caractérisé par un dépôt concentré de l'énergie de la particule à la fin de sa plage de pénétration, un phénomène qui produit un pic, appelé pic de *Bragg* [3] dans la distribution de la perte d'énergie par ionisation. Il s'agit d'une caractéristique importante exploitée en radiothérapie, tel qu'expliqué dans la section 2.3 c).

Les électrons et les positrons, qui sont des particules chargées, en interagissant avec la matière, produisent un processus de *Bremsstrahlung* lorsque leur énergie dépasse un certain seuil appelé énergie critique du matériau. Ce processus consiste en l'émission de photons par une particule chargée accélérée (ou ralentie), en l'occurrence l'électron ou le positon, qui change sa direction dans le champ électrique du noyau. Sous l'énergie critique, les électrons et les positrons interagissent principalement par ionisation directe et excitation du noyau.

Les particules neutres comme les photons et les neutrons dans la matière produisent une sorte d'ionisation qu'on appelle "ionisation indirecte". L'ionisation est produite directement par les particules chargées qui résultent de l'interaction des particules neutres avec la matière.

Selon leur énergie, les photons peuvent interagir via l'effet photoélectrique, qui consiste à extraire un électron de l'atome.

Les photons peuvent également interagir par diffusion *Compton*, qui est un processus de diffusion des photons sur les électrons de la matière. Enfin, les photons dont l'énergie est supérieure à deux fois l'énergie au repos d'un électron, dans la matière, peuvent subir une conversion de production de paires, un processus au cours duquel le photon se transforme en une paire d'électron et de positron en intéragissant avec le champ électrique du noyau.

2.3 Utilisation courante des radioisotopes

Comme expliqué ci-dessus, chaque radio-isotope est caractérisé par un type de rayonnement spécifique, une demi-vie et une pénétration dans la matière. Ces différentes propriétés peuvent être sélectionnées à des fins médicales, à des visées diagnostiques ou thérapeutiques.
On ne trouve que peu d'isotopes instables dans la nature. La plupart d'entre eux sont produits artificiellement avec des cyclotrons, avec des accélérateurs de particules linéaires ou des réacteurs nucléaires, avant d'être soumis à un processus de purification et de préparation à usage médical.

a) Définition d'un radiotraceur et d'un chélateur

Les radio-isotopes, aussi appelés radionucléides, peuvent être liés à différentes molécules pour former un composé radiopharmaceutique (ou radiotraceur). Ces composés sont généralement introduits dans l'organisme par injection ou par ingestion.
Un radiotraceur est une molécule ciblant une fonction ou un récepteur spécifique de l'organisme, marquée par un isotope radioactif, qui se décompose à travers l'émission alpha, bêta ou gamma. L'interaction des produits de désintégration avec la matière est utilisée soit pour produire une image, soit pour détruire une cellule.
Les chélateurs sont de petites molécules qui se lient très étroitement aux ions métalliques pour former un complexe. Ils sont nécessaires pour se lier aux isotopes radioactifs. Un chélateur fréquemment utilisé est le composé macrocyclique connu sous le nom de DOTA (acide 1,4,7,10-tétraazacyclododécane-1,4,7,10-tétraacétique), surtout pour complexer des ions lanthanides. Un autre exemple d'agent chélateur est l'acide

aminopolycarboxyclide DTPA (acide pentetique), qui a une grande affinité pour les cations métalliques.

b) Utilisation actuelle des radioisotopes à visée diagnostique

La scintigraphie, le SPECT (Single Photon Emission Computed Tomography) et le PET (Tomographie à Emission de Positrons) sont des outils de diagnostic spécialisés, qui utilisent des radiotraceurs, permettant de quantifier l'activité métabolique in vivo avec une grande sensibilité. La scintigraphie produit des images bidimensionnelles, tandis que le SPECT et le PET sont des techniques d'imagerie tridimensionnelle. Le PET a une meilleure résolution spatiale que le SPECT. La localisation atomique peut être améliorée en combinaison avec le CT (Computerised Tomography) ou l'IRM (imagerie par résonance magnétique).

- **Scintigraphie**

La scintigraphie utilise le rayonnement gamma. L'un des premiers radiotraceurs émetteurs de rayons gamma utilisés en scintigraphie est l'analogue de la somatostatine ^{111}In-DTPA-Octreotide [4]. Il est utilisé comme outil de diagnostic pour les tumeurs neuroendocrines telles que l'adénome pituitaire, le phéochromocytome, les néoplasies des ilôts pancréatiques, le carcinome pulmonaire à petites cellules et d'autres.

- **Imagerie SPECT**

L'imagerie SPECT utilise également des radiotraceurs avec des émetteurs de rayonnement gamma. Un collimateur ne sélectionne que les photons émis qui arrivent sur le détecteur à un angle perpendiculaire. La détection de la direction gamma permet de localiser la région d'émission et donc de mesurer la concentration du traceur dans une partie donnée du corps.

Une image 3D est obtenue en tournant le détecteur autour du patient. Environ 80 % des études de diagnostic en médecine nucléaire sont réalisées avec du Technétium-99m (^{99m}Tc), un émetteur de photons, utilisé pour l'imagerie de diverses fonctions physiologiques, par exemple la scintigraphie osseuse avec des diphosphonates marqués au ^{99m}Tc, le ^{99m}Tc-sestamibi dans les études de perfusion myocardique, les études de ventilation/perfusion pulmonaire combinant le Technegas et l'albumine radioactive

macroagrégée de technétium (^{99m}Tc-MAA) ou enfin le Pertechnéate (^{99m}Tc-O_4^-), pour les études anatomiques et fonctionnelles de la thyroïde.

Le ^{99m}Tc pourrait également être utile dans l'imagerie du cancer du pancréas. Une étude récente a utilisé des nanoparticules d'Octréotide marquées au ^{99m}Tc, qui ont montré une affinité in vivo pour l'adénocarcinome canalaire induit par MIA Paca-2, mimant une tumeur du pancréas distal à polypeptide pancréatique (Ppome) [5].

Les tumeurs neuroendocrines du pancréas quant à elles peuvent être étudiées avec de l'Octréotide marqué au 99mTc (99mTc-HYNIC-TOC) [6].

Un autre radionucléide important pour l'imagerie SPECT est l'iode radioactif (I), principalement sous forme de ^{123}I pour le diagnostic fonctionnel des maladies thyroïdiennes. En imagerie du cancer du pancréas, une étude a signalé l'usage d'adénovirus mutés aux propriétés oncolytiques marqués au ^{125}I dans des modèles murins [7].

Le ^{99m}Tc et les isotopes de l'iode ont l'avantage d'être facilement accessibles mais ne sont pas fréquemment utilisés pour l'imagerie du cancer du pancréas. Comme nous le verrons plus loin, une variété de nouveaux radio-isotopes à émission d'un seul photon sont d'intérêt pour le diagnostic et le suivi des néoplasies pancréatiques.

- Imagerie PET

L'imagerie PET utilise des traceurs émettant le rayonnement bêta+.

Le traceur émet un positron qui s'annihile en interagissant avec un électron du corps du patient. Cette interaction libère de l'énergie par l'émission de deux rayons gamma de même énergie dans des directions opposées, qui seront ensuite détectés. Les détecteurs sont assemblés sur des supports circulaires autour du patient. Des images tridimensionnelles de la concentration du traceur dans le corps sont ensuite construites par analyse informatique.

Un émetteur ß+ commun pour l'imagerie PET est le Fluor-18 (^{18}F), utilisé pour une variété de traceurs. Un exemple largement connu est le ^{18}F-Fludeoxyglucose (FDG), un analogue du glucose qui joue un rôle important dans la détection du cancer avant et après traitement, les tumeurs présentant généralement un métabolisme du glucose accru [8].

Cependant, le FDG n'est pas un marqueur spécifique des tumeurs et peut également s'accumuler en cas de processus inflammatoire. Dans le cas de l'imagerie du pancréas, plusieurs affections bénignes, comme l'inflammation, l'état postopératoire, l'infection, l'abcès ou l'activité de l'intestin adjacent peuvent faussement mimer une tumeur

maligne. L'hyperglycémie peut entraîner une diminution de l'absorption du FDG en raison d'une inhibition compétitive.

Des études ont montré que le PET au FDG présente un intérêt dans le diagnostic de l'adénocarcinome pancréatique [sensibilité : 0,91 (95 % IC : 0,88-0,93) ; spécificité : 0,81 (95 % IC : 0,75-0,85)] mais ses avantages dans la stadification sont peu clairs [9].

Le mode d'absorption du FDG en imagerie PET/CT pourrait être utile pour distinguer la pancréatite auto-immune de l'adénocarcinome pancréatique, en complément de l'IRM, afin d'améliorer la précision du diagnostic [10].

Les tumeurs neuroendocrines pancréatiques, d'autre part, ont une plus faible avidité au FDG. Par conséquent, seules quelques tumeurs neuroendocrines ayant une activité prolifération élevée et une faible différenciation cellulaire montrent une absorption élevée du FDG au PET/CT [11].

Afin de surmonter les nombreuses limitations du FDG dans l'imagerie du cancer du pancréas, d'autres radiotraceurs prometteurs sont en cours d'évaluation, tel que l'analogue de la thymidine, le 3'-désoxy-3'-^{18}F-fluorothymidine (FLT), un marqueur de prolifération cellulaire, qui a démontré sa capacité à distinguer les tumeurs pancréatiques malignes des pseudotumeurs bénignes, s'accumulant de manière sélective dans les cellules cancéreuses au PET [12]. De plus, ce traceur pourrait jouer un rôle dans la prédiction de la survie chez les patients atteints d'un cancer du pancréas résécable [13].

D'autres radiotraceurs utiles pour l'imagerie PET dans l'adénocarcinome pancréatique ou les tumeurs pancréatiques neuroendocrines seront développés dans la dernière section de cet ouvrage.

c) Utilisation actuelle des radioisotopes à visée thérapeutique

Les radio-isotopes peuvent être sélectionnés pour la thérapie en fonction du type de particules émises dans le processus de désintégration. Les dommages causés par l'interaction de ces particules avec les cellules du corps par ionisation directe ou par les radicaux libres provoquent l'arrêt de la reproduction des cellules cancéreuses. Le rayonnement des radio-isotopes entraîne des dommages irréparables à l'ADN, qui peuvent également affecter les cellules saines qui se trouvent à proximité. Il est donc souhaitable que les radio-isotopes déposent des doses de rayonnement localisées élevées. En conséquence, les isotopes émettant des particules alpha et bêta- de faible énergie sont préférables [14].

- Thérapie Bêta- versus thérapie alpha

En raison de leur faible vitesse et de leur charge électrique plus élevée, les particules alpha déposent dans les tissus une énergie élevée sur une courte distance, ce qui entraîne un transfert d'énergie linéaire élevé et localisé dans le noyau cellulaire [15]. Cela permet une plus grande probabilité de générer des cassures d'ADN double brin dans les cellules cibles, indépendamment de l'oxygénation des tissus, du débit de dose et de la résistance cellulaire à l'irradiation par photons et à la chimiothérapie [16]. Par conséquent, les particules alpha sont hautement cytotoxiques.

Le transfert d'énergie linéaire des particules bêta est inférieur à celui des particules alpha de même vitesse ; par conséquent, une dose plus élevée dans le tissu cible est nécessaire [17].

- La radiothérapie avec des sources radioactives non-scellées

Une méthode de radiothérapie interne est l'utilisation de radiotraceurs liés à des isotopes ayant des propriétés thérapeutiques, une méthode appelée "radiothérapie vectorisée interne" ou “radiothérapie avec des sources radioactives non-scellées”.

Les cellules malignes présentent généralement une surexpression des récepteurs régulateurs. La cellule tumorale peut être localisée en utilisant des peptides spécifiques à ces récepteurs, liés à des isotopes détectés par scintigraphie ou PET. Ces récepteurs peuvent également être ciblés pour le traitement. Le but de la thérapie vectorisée interne est de détruire uniquement la cellule à laquelle le radiotraceur est lié avec un minimum de dommages aux tissus sains.

La théranostique désigne la combinaison du diagnostic et de la thérapie en utilisant le même vecteur dans un radiotraceur et en modifiant le radio-isotope de marquage [18].

Dans les cellules de l'adénocarcinome du pancréas, on observe une surexpression des récepteurs de la neurotensine, qui pourraient être ciblés par un traitement à sources radioactives non-scellées [19]. Une autre cible pour la radiothérapie avec des sources non-scellées concerne les récepteurs à la somatostatine dans les tumeurs neuroendocrines du pancréas [20].

La radioimmunothérapie est une forme spécifique de thérapie vectorisée interne combinée à l'immunothérapie, qui elle même utilise des radionucléides conjugués à des anticorps monoclonaux ou des peptides dirigés contre les tumeurs [21].

Les différentes possibilités avec des sources radioactives non-scellées en thérapie du cancer du pancréas seront d’avantage développées dans le dernier chapitre.

- Brachythérapie

Une autre méthode de radiothérapie interne est la brachythérapie, au cours de laquelle les sources radioactives scellées sous forme d'implants sont insérées directement dans les tissus, par exemple par voie chirurgicale, par endoscopie guidée par ultrasons ou par implantation percutanée sous CT [22]. La source radioactive scellée placée dans la tumeur délivre localement une dose de rayonnement élevée à courte distance, avec une réduction rapide de la dose dans les tissus sains environnants.

Par le passé, la brachythérapie était pratiquée avec une source naturelle de radium. Actuellement, la production artificielle d'isotopes permet d'élargir la gamme des éléments radioactifs disponibles pour la brachythérapie.

Il a été envisagé d'implanter les sources radioactives dans les tissus par la chirurgie minimalement-invasive sous assistance robotique (système Da Vinci). Jusqu'à présent, les expériences ont porté sur des patients atteints de cancer du poumon non à petites cellules [23], de cancer de la prostate [24] ou de cancer de la vessie [25].

La brachythérapie robotisée permet l'insertion d'implants radioactifs avec précision, en minimisant les dommages pour les patients et à une distance sûre pour le chirurgien afin de prévenir l'irradiation. Toutefois, ce domaine nécessite plus de recherche, le nombre d'études portant sur la brachythérapie robotisée étant faible à l'heure actuelle.

- Radiothérapie externe

Nous nous concentrerons dans cette revue de littérature sur l'utilisation des isotopes pour la thérapie par source non scellée et la brachythérapie. Néanmoins, pour des raisons d'exhaustivité, il convient de mentionner que les sources de rayonnement pourraient également être situées à distance du corps du patient, par radiothérapie externe par faisceau (EBRT). La radiothérapie standard utilise des faisceaux de photons et d'électrons à haute énergie.

L'utilisation de particules comme les ions, les protons et les pions est nommée hadronthérapie. Ces particules se comportent dans la matière d'une manière similaire aux particules alpha et produisent un dépôt d'énergie élevé et très concentré à la fin de leur plage de pénétration [14].

Comme dans le cas des particules alpha, ce processus a l'avantage d'un dépôt d'énergie moindre dans le tissu sain entourant le tissu cible. De plus, comme la portée de pénétration de ces hadrons dépend principalement de leur énergie, le fait de varier l'énergie des particules permet de cibler des régions situées à différentes profondeurs

dans le corps.

Dans le traitement de l'adénocarcinome du pancréas, l'EBRT est généralement associée à une chimiothérapie sensibilisante, qui permet d'augmenter la toxicité du rayonnement pour les cellules tumorales [26]. L'EBRT est indiqué pour la thérapie adjuvante après résection chirurgicale en cas de tumeur localisée, pour la thérapie néoadjuvante dans les tumeurs localement avancées ou en traitement palliatif en cas de maladie métastatique.
Cependant, des essais impliquant l'EBRT pour la thérapie du cancer du pancréas ont montré des résultats contradictoires [27]. Ceci est probablement lié à une résistance intrinsèque à la radiothérapie chez les cellules cancéreuses pancréatiques.

Pour surmonter cette limitation, des techniques telles que la technique de la thérapie corporelle stéréotaxique (SBRT) ont été développées. La SBRT permet l'application précise d'une dose élevée de rayonnement à un volume cible limité, ce qui réduit la dose de rayonnement aux tissus sains avoisinants et minimise la toxicité [28]. Une étude rétrospective nationale [29] chez des patients atteints d'adénocarcinome pancréatique non réséqué a montré que la SBRT est associée à de meilleurs résultats que la chimiothérapie avec ou sans EBRT.

Une autre technique visant à administrer une forte dose de radiation tout en réduisant la dose aux tissus sains est la radiothérapie intraopértoire (IORT). Il s'agit d'administrer une haute dose d'irradiation en une fraction unique au cours d'une intervention chirurgicale, ciblant généralement le lit tumoral après résection grossière totale ou la maladie résiduelle restante si la résection complète n'a pas été possible. Les organes à risque peuvent être déplacés hors du champ de rayonnement pour limiter l'exposition au rayonnement.
Dans le cancer du pancréas, l'IORT a été suggérée pour les tumeurs résécables et non résécables afin d'améliorer le contrôle local et la palliation de la douleur [30]. Il est habituellement utilisé après une EBRT préopératoire ou avant une EBRT postopératoire. L'IORT est associée à des taux de récurrence plus faibles [31].

Au fil des années, les progrès dans les domaines de la physique, de l'imagerie médicale, de la robotique, des anticorps monoclonaux et une meilleure connaissance des mécanismes tumoraux ont ouvert de nouvelles voies prometteuses pour le traitement des tumeurs résistantes aux traitements existants. Parallèlement, l'étude et la

découverte de nouveaux isotopes ont suscité un intérêt croissant, ce qui a motivé la construction de nouvelles installations d'accélérateurs dédiées à leur production.

Notre objectif est d'attirer l'attention sur les progrès réalisés en médecine nucléaire en collaboration avec le CERN et sur les applications futures potentielles, en particulier pour le traitement des tumeurs agressives telles que l'adénocarcinome pancréatique, grâce à une analyse approfondie de la littérature.

2. Introduction (English)

2.1 History of nuclear medicine

A milestone in the history of the use of radiation in medicine is the discovery of X-rays by Wihelm Conrad Röntgen in 1895, while he was working with cathode tubes.
This achievement was followed in 1896 by the results of Henri Becquerel who, working with uranium salts, discovered the natural (also called "spontaneous") radioactivity, namely the fact that radiation comes from uranium itself, without any need for excitation by an external energy source. His doctoral student, Marie Curie, later discovered additional radioactive elements: thorium, polonium and radium. Radium soon gained general interest in the treatment of various diseases and also raised public health concerns.
Ernest Rutherford studied the properties of the radioactive decays and named them alpha, beta and gamma in 1899, classifying them by their ability to penetrate matter.
Later it was discovered that the nature of the X-rays and of the gamma radiation is the same: they are electromagnetic radiation, which at quantum level can be described by the emission of neutral particles of zero mass, the photons [1].

It was George de Hevesy who developed the idea that a stable atom in the body might be replaced by the radioactive form of the same element as a tracer. He developed in 1935 the first radioactive tracer by using ^{32}P in animals, for which he was awarded the Nobel Prize for chemistry in 1943 [2].
In 1941, Saul Hertz discovered the use of radioactive iodine for the treatment of thyroïd disease. Today, it is still commonly used in various forms.
^{99}Tc is also very commonly employed. It was first isolated in 1938 and introduced as a medical radiotracer in the 1950s.

In the last hundred years, a variety of new radioactive elements were discovered and are now currently used in the medical field. Advances in nuclear medicine were only possible through the knowledge acquired in physics of the nuclear structure, of the radioactive decays and of the interaction of radiation with matter. These subjects will be treated shortly in the next section.

2.2 Nuclear medicine : basic knowledge and definitions

a) Definition of isotope, alpha, beta and gamma radiation

A nucleus is characterised by the number of protons and neutrons. Nuclei are labelled ${}^{A}_{Z}X$, where X is the chemical symbol of the element. A is the atomic mass number and equals the sum of the number of protons, Z, and neutrons, N. Nuclei with the same atomic number Z and different number of neutrons, are called isotopes. Each atomic number Z identifies a specific element, but an atom of a given element may exist in nature or be produced artificially with a different number of neutrons N, therefore a wide range of isotopes may occur.

Some isotopes are unstable and decay by emitting radiation, and are therefore called radioactive or radioisotope, whereas others are referred as stable isotopes. The radioactive emission can be spontaneous or induced by exposure to a specific radiation. A parent nucleus will emit through disintegration to a daughter nucleus different particles : alpha, beta or gamma.

The alpha radiation is the emission of an alpha particle, which is identical to a nucleus of helium (${}^{4}He^{2+}$), made of 2 protons and 2 neutrons. The electric charge of an alpha particle is therefore two times the electric charge of a proton. After emitting an alpha particle, the atom has its mass number reduced by four and its atomic number reduced by two. The alpha radioactive decay is represented by the following expression :

$${}^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y + {}^{4}_{2}He$$

The beta radiation is classified into various processes : the beta+ decay, the beta- decay and the electron capture. The beta+ decay is characterised by the emission of a positron, which is an antielectron (a particle with the same characteristics of an electron but with opposite electric charge) and a neutrino, as described by the following expression:

$${}^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + ß^{+} + \text{neutrino}$$

The beta- decay consists in the emission of an electron and an antineutrino :

$${}^{A}_{Z}X \rightarrow {}^{A}_{z+1}Y + ß^{-} + \text{antineutrino}$$

Finally, the process of electron capture by the atomic nucleus can also occur represented by:

$^{A}_{Z}X + e^{-} \rightarrow {}^{A}_{Z-1}Y + \text{neutrino}$

The gamma radiation is the emission of a photon by an excited nucleus according to the following expression :

$^{A}_{Z}X^{*} \rightarrow {}^{A}_{Z}X + \text{photon}$

where X* represents the excited form of a nucleus.

Another radioactive process of interest is the internal conversion, an electromagnetic process in which the interaction of the electromagnetic field of an excited nucleus with an orbital electron results in the ejection of the electron from the atom with a discrete energy spectrum.

$^{A}_{Z}X^{*} \rightarrow {}^{A}_{Z}X + \text{electron}$

After the process, the hole left in the electron shell of the atom, is subsequently filled by other electrons that descend to that empty, lower energy level. In this process photons in the domain of the X-ray(s), electron(s) called Auger electrons, or both are subsequently emitted.

A form of radioactive decay is referred to as spontaneous fission, and consists in a process in which the nucleus of an atom splits into smaller, lighter nuclei. These are unstable and give rise to a chain of radioactive decays. The fission often produces also free neutrons and gamma photons, and releases large amount of energy. The spontaneous process occurs especially in very high-mass-number isotopes. The fission can also be induced by a nuclear interation of a neutron with a nucleus.

A radioisotope turns into a stable or unstable daughter nucleus through these different kinds of decays within a characteristic time, which is defined “half-life”. A radioactive compound is characterised by the number of emissions per unit of time, which is called “activity”. The half-life is the time taken for the activity of a given amount of a radioactive substance to decay to half of its initial value.

The daughter nucleus, if unstable, will in turn decay and a cascade process will proceed until, ultimately, stable elements are produced.

b) Interaction of particles with matter

When the final particles of a radioactive decay cross the matter, different mechanisms of interaction between the particles and the atoms of the material take place. After the interaction a particle may slow down or change its direction or be absorbed. If the block of matter is thick enough, a penetration range may be defined for each charged particle depending on the value of its electric charge, its initial energy, and the characteristics of the traversed material.

Electrically charged heavy particles, specifically low energy alpha particles or protons, interact mainly by direct ionization and excitation of the nucleus. The energy deposited by the particle per unit of length (the linear energy transfer) depends on the square of its electric charge and is therefore four times higher for an alpha particle than for a proton of the same velocity. In this process when the total energy of the particle is approximately below three times its rest energy, the linear energy transfer increases steeply when the particle velocity decreases. Consequently this process is characterized by a concentrated deposit of the particle energy at the end of its penetrating range, a phenomenon causing a peak, called the *Bragg* peak [3], in the distribution of the energy loss by ionization. This is an important feature exploited in the radiation therapy, as explained in Section 2.3 c).

Electrons and positrons, which are light charged particles, interacting with matter, produce in prevalence a *Bremsstrahlung* process when their energy is above a certain threshold called the critical energy of the material. This process consists in the emission of photons by an accelerated (or decelerated) charged particle, in this case the electron or positron, which changes its direction in the electric field of the nucleus. Below the critical energy electrons and positrons interact mainly by direct ionization and excitation of the nucleus.

Neutral particles as photon and neutrons in matter produce a kind of ionisation that is called “indirect ionisation”. The ionisation is produced directly by the charged particles that result from the neutral particle interaction with matter.

Depending on their energy, photons can interact via the photoelectric effect, which consists in the extraction of an electron from the atom.

Photons can also interact via *Compton* scattering, which is a diffusion process of photons on the electrons of the matter. Finally, photons with energy above two times the rest

energy of an electron, in matter, can undergo a pair production conversion, a process in which the photon converts into a pair of electron and positron by taking energy from the electric field of the nucleus.

2.3 Current uses of radioisotopes

As explained above, each radioisotope is characterised by a specific radiation type, half-life and penetration through matter. These different properties can be selected for medical use, either for diagnosis or for therapy.
Only few unstable isotopes are found in nature. Most of them are artificially produced with cyclotrons, linear particle accelerators or with nuclear reactors, before going through a purification and preparation process for medical use.

a) Definition of a radiotracer and chelator

The radioisotopes, also called radionuclide, can be linked to different molecules to form a radiopharmaceutical compound (or radiotracer). These compounds are usually introduced into the body by injection or by ingestion.
A radiotracer is a molecule targeting a specific function or receptor in the body, labelled by a radioactive isotope, which will decay through alpha, beta or gamma emission. The interaction of the decay products with matter is used either to produce an image or to destroy a cell.
Chelators are small molecules that bind very tightly to metal ions to form a complex. They are necessary to bind to the radioactive isotopes. A frequently used chelator is the macrocyclic compound known as DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), especially for the complexion of lanthanide ions. Another example of chelating agent is the aminopolycarboxyclid acid DTPA (pentetic acid), which has a high affinity for metal cations.

b) Radioisotopes for diagnostic imaging

Scintigraphy, SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography) are specialised diagnostic tools, which make use of radiotracers, allowing metabolic activity quantification in vivo with high sensitivity. Scintigraphy produces two-dimensional images, whereas SPECT and PET are three-dimensional imaging techniques. PET has a better spatial resolution than SPECT. The anatomical localisation can be improved when combined to CT (Computerised Tomography) or MRI (Magnetic Resonance Imaging).

- Scintigraphy

Scintigraphy makes use of gamma radiation. One of the first gamma emitting radiotracers used for scintigraphy is the somatostatin analogue ^{111}In-DTPA-Octreotide [4]. It is used as a diagnostic tool for neuroendocrine tumors such as pituitary adenoma, carcinoid pheochromocytoma, pancreatic islet cell tumor, small cell lung carcinoma and others.

- SPECT imaging

SPECT imaging also uses radiotracers with gamma radiation emitters. A collimator selects only those emitted photons that arrive on the detector at an angle nearly perpendicular. The detection of the gamma direction allows the localisation of the emission region and therefore the measurement of the tracer concentration in a given part of the body.

A 3D image is obtained by turning the detector around the patient. About 80% of nuclear medical studies in diagnosis are performed with Technetium-99m (^{99m}Tc), a photon emitter, used for imaging of various physiological functions, for example bone scintigraphy with ^{99m}Tc labelled diphosphonates, ^{99m}Tc-sestamibi in myocardic perfusion studies, pulmonary ventilation/perfusion scans with Technegas and radioactive Technetium macro aggregated albumin (^{99m}Tc-MAA) or Pertechneate (^{99m}Tc-O_4^-) for anatomical and functional thyroid studies. ^{99m}Tc might even be of use in pancreatic cancer imaging, as a recent study used ^{99m}Tc-labeled octreotide nanoparticles, which showed in vivo affinity for MIA Paca-2 inducted ductal adenocarcinoma, mimicking pancreatic polypeptide-secreting tumor of the distal pancreas (Ppoma) [5].

As for pancreatic neuroendocrine neoplasm studies, they can be performed with ^{99m}Tc-labeled octreotide (^{99m}Tc-HYNIC-TOC) [6].
Another important radionuclide for SPECT imaging is radioactive Iodine (I), mostly in the form of ^{123}I for functional diagnosis of thyroid disease. In pancreas cancer imaging, there have been reports of SPECT/CT in vivo imaging with ^{125}I labeling oncolytic adenoviral mutants in murine models [7].
^{99m}Tc and ^{125}I have the advantage of being easily available but aren't frequently used for pancreatic cancer imaging. As it will be discussed further, a variety of other new radioisotopes with single photon emission are now of interest for the diagnosis and follow-up of pancreatic neoplasms.

- PET imaging

PET imaging uses tracers with beta+ decay properties. The tracer emits a positron, which will annihilate by interacting with an electron of the patient's body. This interaction releases energy through the emission of two gamma rays of same energy in opposite directions, which will then be detected. The detectors are assembled in buckets mounted on circular supports around the patient. Three-dimensional images of tracer concentration in the body are then constructed by computer analysis.

A common beta+ emitter for PET imaging is Fluorine-18 (^{18}F), used in a variety of tracers. A widely known example is ^{18}F-Fludeoxyglucose (FDG), a glucose analog, which plays an important role in the detection of cancer, before and after treatment, as tumors usually show increased glucose metabolism [8].
However, FDG isn't tumor-specific and can accumulate inside inflammatory cells as well. In the case of pancreatic imaging, several benign conditions, such as inflammation, post-operative status, infection, abscess or adjacent bowel activity can mimic malignancies. Hyperglycemia can lead to a drecreased absorption of FDG due to competitive inhibition. Reviews have shown that PET with FDG is still valuable in the diagnosis of pancreatic adenocarcinoma [sensitivity: 0.91 (95%CI: 0.88-0.93); specificity: 0.81 (95%CI: 0.75-0.85)] but its benefits in staging are unclear [9].
The FDG uptake pattern in PET/CT imaging might be usefull to differentiate autoimmune pancreatitis from pancreatic adenocarcinoma, as a finding supplement to MR, to improve de diagnostic accuracy [10].
Pancreatic neuroendocrine tumors on the other hand, have a lower FDG-avidity. Therefore, only a few neuroendocrine tumors with high proliferative activity and low

differentiation show a high FDG uptake on PET/CT [11].

To overcome the several limitations of FDG in pancreatic cancer imaging, other promising radiotracers are being evaluated, such as the thymidine analog 3'-deoxy-3'-^{18}F-fluorothymidine (FLT), a marker for cell proliferation, which has shown to be able to differentiate malignant pancreatic tumors from benign pseudotumours, by being uptaken selectively in malignant tumors on PET [12]. Furthermore, this tracer might play a role in predicting survival in patients with resectable pancreatic cancer [13]. Other radiotracers useful for PET imaging in pancreatic adenocarcinoma or neuroendocrine pancreatic tumors will be further developped in the last section.

c) Current uses of radioisotopes for therapeutics

Radioisotopes can be selected for therapy according to the type of emitted particles in the disintegration process. The damage inflicted by the interaction of these particles with body cells through direct ionisation or free radical damage causes the cancerous cells to stop reproducing. The radiation of the isotopes leads to irreparable DNA damage, which can affect also bystander healthy cells. For this purpose, it is desirable that radioisotopes deposit localised high radiation doses, consequently isotopes emitting alpha and low energy beta- particles are preferred [14].

- Beta- versus alpha therapy

Due to their low velocity and higher electric charge, alpha particles deposit in tissue high energy within a short range, resulting in high and localised linear energy transfer in cell nuclei [15]. This allows a greater probability of generating DNA double-strand breaks in target cells, independently of tissue oxygenation, dose rate and cellular resistance to photon irradiation and chemotherapy [16]. Therefore, alpha particles are highly cytotoxic.

The linear energy transfer of beta particles is lower than that of alpha particles of same velocity; consequently an higher dose within the targeted tissue is needed [17].

- Unsealed source therapy

A method of internal radiation therapy is the use of radiotracers linked to isotopes with

therapeutic properties, a method called “unsealed source therapy”.

Malignant cells generally present an over-expression of regulatory receptors. The tumor cell can be localised by using peptides specific to these receptors, linked to isotopes detected by scintigraphy or PET. Such receptors can also be targeted for treatment. The aim of unsealed source therapy is to destroy only the cell to which the radiotracer is bound with minimal damage to healthy tissue.

The term theranostics indicates the combination of diagnosis with therapy by using the same vector in a radiotracer and changing the labelling radioisotope [18].

In pancreatic adenocarcinoma cells, there is an over-expression of neurotensin receptors, which could be targeted by unsealed source therapy [19]. Another target for unsealed source therapy are the somatostatin receptors for neuroendocrine pancreatic tumors [20].

Radioimmunotherapy is a specific type of unsealed source therapy combined with immunotherapy, that uses radionuclides conjugated to tumor-directed monoclonal antibodies or peptides [21].

We will develop the possibilites of unsealed source in pancreatic cancer imaging and therapy in the last section.

- Brachytherapy

Another method of internal radiation therapy is brachytherapy, in which sealed radioactive sources in the form of implants are inserted directly into the tissue, for example surgically, by ultrasound-guided endoscopy or by CT-guided percutaneous implantation [22]. The sealed radioactive source placed into the tumor will locally deliver a high radiation dose at short distance, with rapid dose fall-off in the surrounding healthy tissue.

In the past, brachytherapy was performed with natural radium. Currently, the artificial production of isotopes allows a wider range of radioactive elements available for brachytherapy.

It has been considered to implant radioactive sources within the tissues with minimally invasive surgery under robotic assistance (Da Vinci system). So far, it has been experimented in patients with non-small cell lung cancer [23], with prostate [24] or with bladder cancer [25].

Robot-assisted brachytherapy allows the insertion of radioactive implants with precision, with minimal damage for the patients and at a safe distance for the surgeon to prevent irradiation. However, further studies need to be developed.

- **Ion Beam Therapy**

We will focus on the use of isotopes for unsealed source therapy and brachytherapy, but for the sake of completeness, it should be mentioned that sources of radiation could also be located at a distance from the patient body, through external beam radiotherapy (EBRT). The standard radiation therapy uses high energy photon and electron beams.
The use of particles like ions, protons and pions is called hadron therapy. These particles behave in matter in a way similar to the alpha particles and produce a high and very concentrated deposit of energy at the end of their penetrating range [14].
As in the case of the alpha particles, the advantage of this behaviour is that the energy deposition profile is such that less energy is deposited into the healthy tissue surrounding the target tissue. In addition, since the penetrating range of these hadrons depends mainly on their energy, varying the particle energy allows targeting regions situated at different depths in the body.

In pancreatic adenocarcinoma therapy, EBRT is usually associated with sensitising chemotherapy, increasing the toxicity of radiation to tumors cells [26]. Indications include adjuvant therapy after surgical resection in localised resectable adenocarcinoma, neoadjuvant therapy in locally advanced tumors or palliative radiotherapy in metastatic disease.

However, trials involving EBRT have shown conflicting results [27], because of the intrinsic radio resistance of pancreatic cancer cells.
To overcome this limitation, the technique of stereotactic body therapy (SBRT) has emerged, allowing the precise application of high-dose radiation to a limited target volume, which reduces the radiation dose to adjacent healthy tissue and minimises toxicity [28]. A nationwide retrospective study [29] in patients with unresected pancreatic adenocarcinoma showed that SBRT is associated with better outcomes than chemotherapy with or without EBRT.

Another technique aimed to deliver a hight dose of radiation therapy while reducing the dose to healthy tissue is intraoperative radiation therapy (IORT). It consists in the application of a single fraction of high dose irradiation during a surgery, targeting usually the tumor bed after gross total resrction or the remaining residual disease if resection was not completely possible. Organs at risk can be moved out of the radiation field to limit exposure form radiation.
In pancreatic cancer, IORT has been suggested for resectable and unresectable tumors

to improve local control and palliation of pain [30]. It is usually used as a boost after preoperative or prior to postoperative EBRT. It has been reported that IORT is associated with lower recurrence rates [31].

Over the years, the advances in the field of physics, medical imagery, robotics, monoclonal antibodies and a better knowledge of tumor mechanisms have opened new promising ways for the treatment of tumors resistant to the existing therapies. In parallel the study and the discovery of new isotopes has gained an increasing interest motivating the construction of new dedicated accelerator facilities for their production.
Our aim is to bring attention to the advances made in nuclear medicine in collaboration with CERN and the potential future applications, in particular for treatment of aggressive tumors such as pancreatic adenocarcinoma, through an extensive review of literature.

3. Production d'isotopes au CERN (résumé français)

L'Organisation européenne pour la recherche nucléaire (CERN), a été fondée en 1954 et compte aujourd'hui 22 États membres. Sa mission principale est d'étudier les lois qui régissent la structure fondamentale de l'univers en analysant les constituants de base de la matière, les particules fondamentales et les interactions entre celles-ci. Cette activité de recherche s'est accompagnée de plusieurs autres découvertes, qui ont acquis une grande importance pour la société. L'invention du World Wide Web et le développement d'outils de diagnostic pour des applications médicales comme la tomographie par émission de positrons (TEP ou PET, en anglais) au début des années 1990, en collaboration avec les Hôpitaux universitaires de Genève, en sont des exemples bien connus.

L'installation ISOLDE (Isotope mass Separator Online Device) du CERN est dédiée à la production d'une grande variété de faisceaux d'ions radioactifs pour de nombreuses expériences dans le domaine de la physique nucléaire et de la physique des solides, mais aussi dans les sciences du vivant. Les premières expériences d'ISOLDE ont commencé il y a 50 ans. Aujourd'hui, plus de 1300 isotopes radioactifs de 70 éléments différents (Z=2 à 88) avec des demi-vies allant de quelques jours à quelques millisecondes sont produits à des intensités allant jusqu'à 1011 atomes par microA de faisceau de protons, en utilisant le faisceau de protons du Proton-Synchrotron Booster (PSB) du CERN [17].
ISOLDE reçoit environ 50% de tous les protons PSB du CERN, dont 85% traversent la cible ISOLDE sans aucune interaction[17].

CERN-MEDICIS (Medical Isotopes Collected from ISOLDE) est un projet visant à récupérer le faisceau de protons perdu pour produire des radio-isotopes à des fins médicales. Différents types de cibles sont placées derrière la cible ISOLDE, en tirant parti du faisceau de protons restant avant qu'il n'atteigne la décharge du faisceau. Le projet a démarré en 2013, lors d'une période d'arrêt de l'accélérateur au CERN, permettant la modernisation de l'installation ISOLDE et l'extension de son bâtiment pour accueillir l'infrastructure CERN-MEDICIS.

Le projet CERN-MEDICIS est pluridisciplinaire, mettant à contribution des ingénieurs, des physiciens, des chimistes et des médecins, en étroite collaboration avec l'Ecole Polytechnique Fédérale de Genève (EPFL), les Hôpitaux Universitaires de Genève (HUG), le Centre Hospitalier Universitaire de Lausanne (CHUV) et d'autres universités en Europe. Le séparateur de masse isotopique a été donné par l'Université catholique de Louvain. Quinze doctorants de différents pays travaillent actuellement sur le projet.

L'infrastructure de CERN-MEDICIS peut produire une large gamme de radio-isotopes, y compris des émetteurs de positrons, des émetteurs alpha, des émetteurs d'électrons Auger et des émetteurs d'électrons de conversion. Diverses espèces chimiques, telles que les lanthanides, les halogènes, les métaux de transition et les métaux alcalino-terreux, seront disponibles.

Le Terbium est un lanthanide de grand intérêt, avec un fort potentiel théranostique grâce à la variété de ses radio-isotopes disponibles au CERN-MEDICIS, qui pourraient, selon leurs propriétés, être exploités pour le diagnostic et/ou le traitement du cancer. Cette caractéristique pourrait être exploitée en particulier pour le traitement des cancers agressifs avec des modalités de traitement limitées, comme l'adénocarcinome pancréatique.

3. Isotope production at CERN

3.1 About CERN and ISOLDE

The European Organisation for Nuclear Research (CERN) was founded in 1954. Today CERN has 22 member states. Its main mission is to probe the fundamental structure of the universe by studying the basic constituents of matter, the fundamental particles, and the interactions among them. This research activity has been accompanied by several spin-offs, which have acquired a great importance for the society. Well-known examples are the invention of the World Wide Web and the development of diagnostic tools for medical applications such as the positron emission tomography (PET) in the early 1990s, in collaboration with Geneva University Hospitals.

The Isotope mass Separator Online Device (ISOLDE) facility at CERN is dedicated to the production of a large variety of radioactive ion beams for many different experiments in the field of nuclear and solid-state physics but also in life sciences. The first experiments at ISOLDE started 50 years ago. Now over 1300 radioactive isotopes of 70 different elements (Z=2 to 88) with half-lives from days down to milliseconds are produced at intensities up to 10^{11} atoms per microA of proton beam, using the proton beam from the Proton-Synchrotron Booster (PSB) at CERN [32]. The CERN's Accelerator Complex is shown in Figure 1.

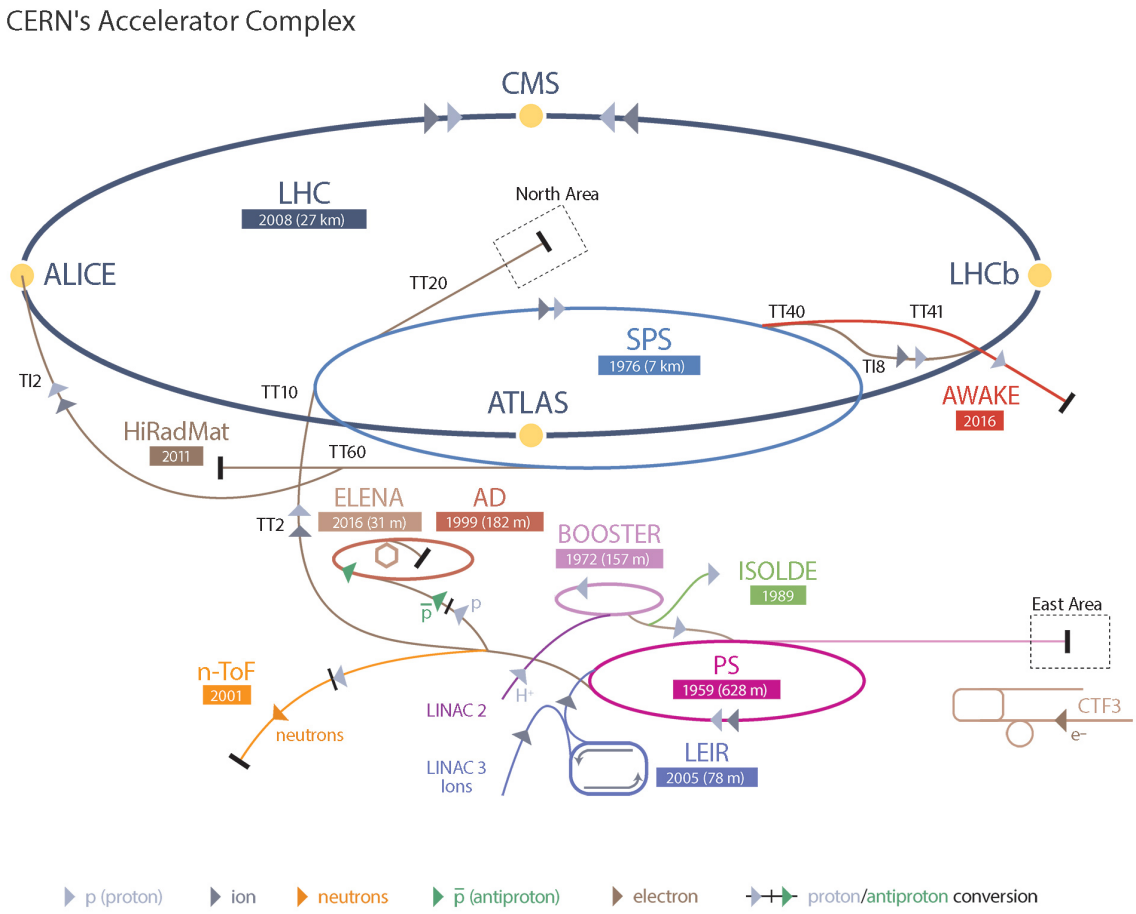


Figure 1. CERN's Accelerator Complex [33].

At ISOLDE, radioactive nuclei are produced by spallation, fission or fragmentation reactions, namely via processes in which a high energy, high intensity proton beam from the PSB is projected on a target, for example a sheet of titanium folded in form of a stacked roll [34] at high temperature. The collision between the beam and the target produces different radioactive fragments. The volatile nuclear reaction products are released from the target into an ion source and are extracted as an intense radioactive ion beam. This production device is coupled to electromagnetic mass spectrometers, which select ion beams of high isotopic and often isobaric purity.

ISOLDE produces a variety of isotopes including uncommon radioisotopes, with a wide range of types and energy of radiation, half-life and chemical properties. The preparations obtained at ISOLDE are of high purity [35].

The first bridge between the radioactive beam and the medical use was the production of Thulium-167 (^{167}Tm) associated to citrate, to perform a PET image of a lymphoma in

the late 1970s [36]. Since then, many more radioactive isotopes of medical interest were produced at ISOLDE. During the 80s, a generator of Rubidium-81 (^{81}Rb) and its daughter radionuclide Krypton-81m (^{81m}Kr) was developed for medical purposes [37]. ^{81m}Kr is a radioisotope with a very short half-life, low radiating for the patient, ideal for lung ventilation studies [38].
In the 90s, the biodistribution of different radiolanthanides through the chelator EDTMP (ethylenediamine tetramethylene phosphonic acid) was studied on tumor-bearing mice [39]. Later on, two positron emitters Yttrium-86 (^{86}Y) and Samarium-142 (^{142}Sm) where collected, chelated with EDTM and used in rabbits at the HUG radiology department for PET quantitative bone imaging [35]. In 1995, monoclonal antibodies with specific tumor homing properties labelled with radiolanthanides and Actinium-225 (^{225}Ac) where injected in colorectal tumor-bearing mice, demonstrating a high uptake in tumor cells [40].
The first in vivo experiment demonstrating the effect of unsealed source therapy using Terbium-149 (^{149}Tb), an alpha emitter, took place at the HUG in 2001 [41].

Therefore, the ISOLDE facility, through its rich radioisotope production, enabled many studies and progresses in the biomedical field, though it wasn't its original purpose. The need of a specific facility dedicated to radioisotope production for biomedical research soon emerged.

3.2 The CERN-MEDICIS facility

ISOLDE receives about 50% of all CERN PSB protons, from which 85% traverse the ISOLDE target without any interaction [32].
The CERN-MEDICIS (Medical Isotopes Collected from ISOLDE) is a project aiming to recover the lost proton beam to produce radioisotopes for biomedical purposes. Different types of targets are placed behind the ISOLDE target, taking advantage of the remaining proton beam before it reaches the beam dump. The project started in 2013, during an accelerator shutdown period at CERN, enabling an upgrade of the ISOLDE facility and an extension of its building to host the CERN-MEDICIS infrastructure.
Several specialists from different academic disciplines contribute to the CERN-MEDICIS project, including engineers, physicists, chemists and doctors. The facility collaborates with the Swiss Federal Institute of Technology (EPFL), the University Hospital of Geneva

(HUG), the University Hospital of Lausanne (CHUV), and other universities in Europe. The isotope mass separator was donated by the catholic University of Leuven. Fifteen PhD students across different countries are currently working on the project.

CERN-MEDICIS equipment includes a rail conveyor system for target transportation from the ISOLDE irradiation area to a shielded decay area, a robot for remote handling and a bunker equipped with a mass separator [36].

The CERN-MEDICIS target is placed behind the ISOLDE target [Fig 2]. It consists in a small cylinder, which can contain a variety of materials, for example ceramics or titanium foils, according to the chosen isotope production.

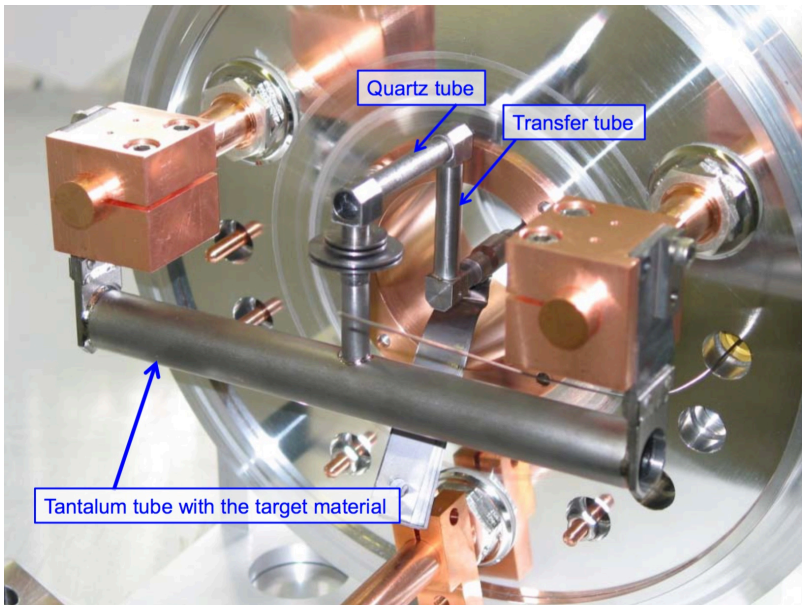


Figure 2. An ISOLDE target unit. Photo courtesy of : [42]

The proton beam hits the target, producing a variety of new elements. A thick wall of iron is placed behind the CERN-MEDICIS target to absorb any remaining beam to avoid uncontrolled isotope diffusion in nature. The target is then transported through rails and handled by a robotic arm, closely monitored by remote computers through cameras, to avoid human irradiation. The target is transported to armoured bunkers for isotope extraction [Fig 3].

To select the production of a specific radioisotope (for example ^{131}I, eliminating ^{123}I and other isotopes), the elements inside the target need to undergo a physical then a chemical purification. Physical purification is enabled by mass spectrometry. The elements are accelerated by an electrostatic force before entering a dipole magnet. The

radioactive ions are deflected in arcs of different radii according to their masses: the heavier the isotope, the longer is the radius of curvature of the arc. Selective windows are used to filter out the unwanted isotopes.

The radioisotope then undergoes a chemical purification step by using a chelator. Subsequently, the batches are checked and ready to be shipped weekly to different institutes and hospitals [32].

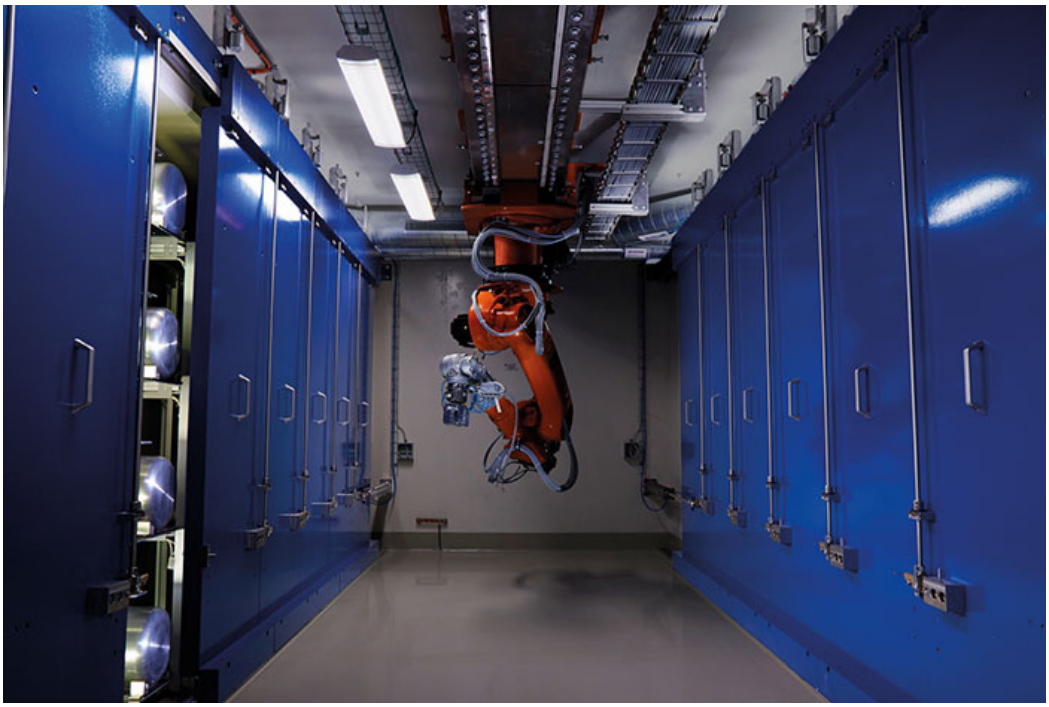
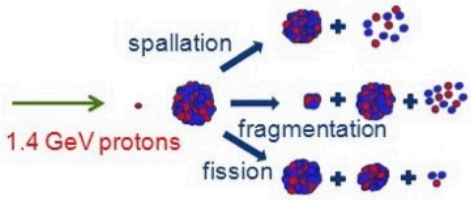


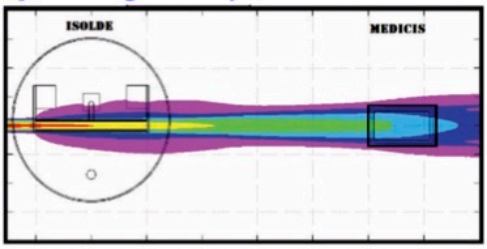
Figure 3. Robot for remote hangling (in the center) and the storage shelves for ISOLDE and CERN-MEDICIS targets. Photo courtesy of : [36].

A summary of the different steps of the isotope production in the CERN-MEDICIS facility is shown in Figure 4.

STEP 1 : IRRADIATION

The proton beam hits the ISOLDE target, producing a variety of new elements.





The CERN-Medicis Target is placed behind the ISOLDE Target, recovering the lost proton beam from ISOLDE for further radioisotope production.

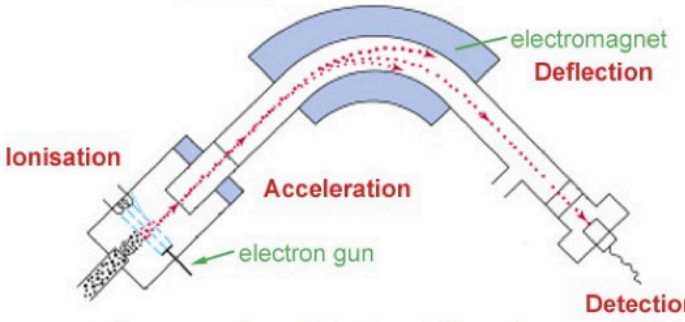
↓

STEP 2 : TRANSFER

The target is transport through a rail conveyor system (arrow showing a target unit)

↓

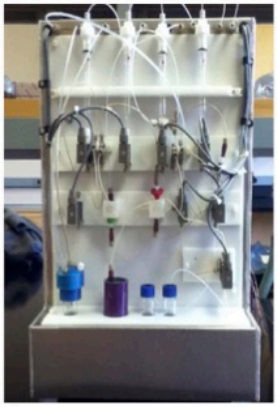
STEP 3 : MASS SEPARATION



Mass spectrometry : ions that are too heavy bend too little, whereas ions that are too light bend too much. Only ions of the right mass enter the detector.

↓

STEP 4 : CHEMICAL PURIFICATION



Automated isotope purification through a remote separation system.

↓

STEP 5 : SHIPPING to different institutes and hospitals.

Figure 4. The CERN-MEDICIS cycle. Images and photos courtesy of : [43][32][36][44][45]

3.3 New isotopes of interest

CERN-MEDICIS can produce a wide range of radioisotopes, including positron emitters, alpha emitters, Auger and conversion electron emitters. Various chemical species, such as lanthanides, halogens, transition metals and alkaline earth metals will be available.

Isotope	Half-life	Medical application	Extracted activity (Bq)	Example of applications [citation]
^{212}Bi	60.6 m	Alpha, beta therapy, SPECT	2.5 E9	Osteoblastic osteosarcoma (P)[46]
^{213}Bi	45.6 m	Alpha, beta therapy	4.2 E8	Metastatic breast cancer therapy (P) [47]
^{177}Lu	6.7 d	Beta- therapy	1.7 E8	Metastatic pancreatic adeno-carcinoma therapy (C)[48] and prostate cancer therapy (C)[49]
^{166}Yb	56.7 h	Auger therapy	1.1 E10	-
^{166}Ho	25.8 h	Beta therapy	6.0 E6	Radioembolisation of neuro-endocrine tumors (C)[50]
^{149}Tb	4.1 h	Alpha therapy	2.4 E10	Folate receptor targeted therapy (P)[51]
^{152}Tb	17.5 h	PET	2.2 E10	Metastatic neuroendocrine tumor imaging (C)[52]
^{155}Tb	5.33 d	SPECT	6.8 E8	Imaging of various tumor xenografts (P)[53]
^{156}Tb	5.35 d	PET	1.3 E7	-
^{161}Tb	6.9 d	Beta-/Auger therapy	5.4 E6	Ovarian cancer therapy (P)[54]
^{153}Sm	46.8 h	Beta therapy	1.0 E9	Skeletal metastases pain palliation (C)[55]
^{140}Nd	3.4 d	PET/Auger therapy	4.0 E9	Neuroendocrine tumor imaging (P)[56]
^{82}Sr	25.5 d	PET	4.0 E8	-
^{89}Sr	50.5 d	Beta therapy	5.4 E8	Skeletal metastases pain palliation (C)[57]
^{71}As	65.3 h	PET	1.6 E9	-
^{72}As	26.0 d	PET	3.0 E9	-
^{74}As	17.8 d	PET	9.0 E7	Vascular imaging of solid tumors (P)[58]
^{77}As	38.8 h	Beta therapy	1.4 E9	Radioimmunotherapy targeting vascular entothelial cells in solid tumors (P)[58]
^{61}Cu	3.3 h	PET	4.0 E9	Fibrosarcoma imaging (P)[59]
^{64}Cu	12.7 h	PET	3.6 E9	Imaging of HER2+ breast cancer (C)[60]
^{44}Sc	4 h	PET	3.2 E10	Metastatic prostate cancer imaging (C)[61]
^{47}Sc	3.4 d	Beta therapy	1.2 E10	Folate receptor targeted therapy (P)[62]
^{11}C	20.3 m	PET	4.2 E9	Image-guided nodal biopsy in recurrent prostate cancer (C)[63]

Table 1. Isotope production at CERN-MEDICIS (non exhaustive list) [32] and potential applications found in the literature (non exhaustive list). (P) : preclinical studies, (C) : clinical studies.

Table 1 shows an example of isotope production at CERN-MEDICIS and potential clinical applications.

Lanthanides include 14 elements with atomic numbers between 58 and 71, and have been of particular interest for radionuclide therapy. These metal ions are chemically similar, having about the same radius, and allow different decay modes. Here we will focus on two particular lanthanides available for production at CERN-MEDICIS : Lutetium and Terbium.

a) Lutetium-177

Lutetium-177 (^{177}Lu) is a low-energy beta- emitting lanthanide. It has been used to label somatostatin analogs in the form of ^{177}Lu-DOTATATE (^{177}Lutetium-DOTA-Octreotate) for the treatment of neuroendocrine tumors [15] [64].
^{177}Lu has also been used in a variety of other in vivo applications. For instance, ^{177}Lu-labelled PSMA (Prostate-specific membrane antigen) is a promising new therapeutic option in patients with metastatic castration-resistant prostate cancer [49]. It's half-life of 6.65 days allows a longer time period to radiolabel and purify ^{177}Lu-labelled radiopharmaceuticals. It's longer half-life may also be useful to label slow targeting antibodies. ^{177}Lu has low photon emission, therefore a lower normal tissue irradiation. The ratio of dose absorption in tumor versus normal tissue is high [65]. The mean penetration range of the emitted beta- particles in soft tissue is relatively short, allowing high energy delivery irradiation to small volumes [66]. This feature could allow effective irradiation of micrometastases or residual tumor tissue.

b) Terbium (^{149}Tb, ^{152}Tb, ^{155}Tb, ^{156}Tb ,^{161}Tb)

Terbium is also an interesting lanthanide, with various isotopes : ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{156}Tb and ^{161}Tb. Terbium can form a stable compound associated with macrocyclic chelators such as DOTA [67].

^{149}Tb has been suggested as a suitable isotope for targeted alpha therapy. It decays with a half-life of 4.1 hours, emitting short-range alpha-particles, gamma-rays and positrons, thus being suitable for SPECT and PET as well [51]. As previously mentioned, the first in vivo experiment demonstrating the effect of unsealed source therapy using ^{149}Tb, took place at the HUG in 2001 [41]. Rituximab was labelled with ^{149}Tb produced at the ISOLDE facility, and then injected in immunodeficient leukemia-bearing mice. Results showed a tumor-free survival for > 120 days in 89% of treated animals, whereas all control mice developed lymphoma disease. This study is a successful example of radioimmunotherapy, combining in one radiopharmaceutical the properties of immunotherapy with those of unsealed source therapy.

^{149}Tb produced at the ISOLDE facility, has already been used in vitro and in vivo in folate receptor (FR) targeted alpha-therapy studies [51]. The folate receptor is expressed in many cancer types, for example ovarian and lung cancer, and has a high affinity for folic acid. Mice bearing tumor with FR-positive cancer cells were injected with ^{149}Tb labelled DOTA-folate conjugate (^{149}Tb-cm09). Results showed significant tumor growth delay and an increased survival time compared to untreated control mice. The mice treated showed no signs of acute kidney or liver toxicity over the time of investigation.

^{152}Tb and ^{155}Tb are suitable for imaging purposes via PET and SPECT, respectively. ^{152}Tb decays with a half-life of 17.5 hours, through electron capture, by emitting positrons and gamma-rays, without the emission of alpha or beta- particles. DOTA associated with octreotide (DOTANOC) labelled with ^{152}Tb, has been used for targeting the somatostatin receptor in tumor-bearing mice, showing good visualisation of tumor xenografts on PET/CT scans [68]. A recent study [52] used ^{152}Tb for the first time in a human, who had a metastatic neuroendocrine neoplasm. The long half life of ^{152}Tb allowed transportation from the ISOLDE facility over several hundreds of kilometers across Europe. Results showed successful PET/CT imaging using ^{152}Tb-DOTATOC, allowing the visualisation of even small metastases.

^{155}Tb decays with a half-life of 5.33 days, through electron capture, while emitting gamma-radiation. Imaging studies have been performed in nude mice bearing tumor xenografts using a SPECT/CT scanner after injection of ^{155}Tb-DOTATATE and ^{155}Tb-MD [53], showing excellent visualisation of the tumor xenografts. The relatively long half-life of ^{155}Tb allowed SPECT imaging even several days after administration.

^{156}Tb is a beta+ emitter with a half-life of 5.35 days, and could therefore be suitable for PET but it has never been tested in vitro nor in vivo.

^{161}Tb decays with a half-life of 6.9 days, emitting beta- particles and Auger electrons. It offers low energy beta- emission similarly to ^{177}Lu, but has the advantage of having various radioisotopes suitable for pretreatment imaging and dosimetry through PET or SPECT [69]. ^{161}Tb can be well stably linked to various molecules as well, using for example the chelator DOTA [67]. ^{161}Tb has also low photon emission, minimising normal tissue irradiation [54]. Various studies showed that ^{161}Tb effectively delivers high doses to small volumes [70][71], proving that it might be an ideal theranostic radionuclide for the labelling and treatment of micrometastases or minimal residual cancer tissue.
A study with ^{161}Tb-labelled antibodies targeting the L1 cell adhesion molecule (L1CAM) in mice bearing ovarian cancer showed high tumor uptake on SPECT, with low level of uptake in other organs. Moreover, this study showed that anti-L1CAM radioimmunotherapy is more effective with ^{161}Tb than with ^{177}Lu [54].

Therefore, Terbium has a high theranostic potential through its variety of radioisotopes available at the CERN-MEDICIS facility, which could be exploited for cancer diagnosis and/or treatment according to the chosen isotope.
This feature could be exploited in particular for the therapy of aggressive cancers with limited treatment modalities, such as pancreatic adenocarcinoma.

4. Applications

4.1 General applications

After radioisotope production at CERN-MEDICIS and purification, the batches are ready to be shipped to different institutes and hospitals.
Currently a team at the nuclear medicine department of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne receives regularly batches of Tb (^{149}Tb, ^{152}Tb, ^{161}Tb) ready for tests in vitro and in vivo in immunodeficient mices. In between shipments of Tb, experiments at CHUV are done with the more frequently available beta+ emitting radioisotope Gallium-68 (^{68}Ga) which can be easily detected by microPET. The final goal is to bring radioisotopes with theranostic properties such as ^{149}Tb to the clinic.

At CHUV, a peptide known to be an effective tumor marker, such as a neurotensin or bombesin analog, is labelled by the radioisotope through a chelator, usually DOTA. Human tumor cells are grafted in subcutaneous tissue of imunodeficient mices for in vivo studies. The radiopharmaceutical is then injected in the mices.
A microPET is available at CHUV to detect the activity of the radiopharmaceutical in several organs of the mices. Radiopharmaceutical biodistribution, specific tumor binding and pharmacokinetics are examined as well as tumor growth and mice survival rates. The final goal is to develop new radiopharmaceuticals that can be used for imaging and therapy purposes.
Up to now, three different neurotensin and two bombesin analogs were radiolabelled and tested at CHUV, in collaboration with CERN physicists, in various tumor models such as colorectal, prostate and pancreatic tumors [72][73]. All analogs showed satisfying tumor uptake and specificity.
A preliminary experiment at CHUV involved ^{152}Tb, an emitter of positrons, coupled with the bombesin analog DOTA-RM6 to target prostate cancer in immunodeficient mice grafted with the human prostate cancer PC-3 cells [74]. One hour after injection, ^{152}Tb-DOTA-RM6 showed a strong and specific uptake in prostate cancer cells [Figure 5]. The three hour biodistribution showed the same radiopeptide retention and specificity in the tumor. However, aside from the tumor, the pancreas showed a strong uptake. The

pancreas and the kidneys, which express the GRP (Gastrin Releasing Peptide) receptor, are at risk of toxicity if the radiotracer's doses are increased for therapeutic purposes.

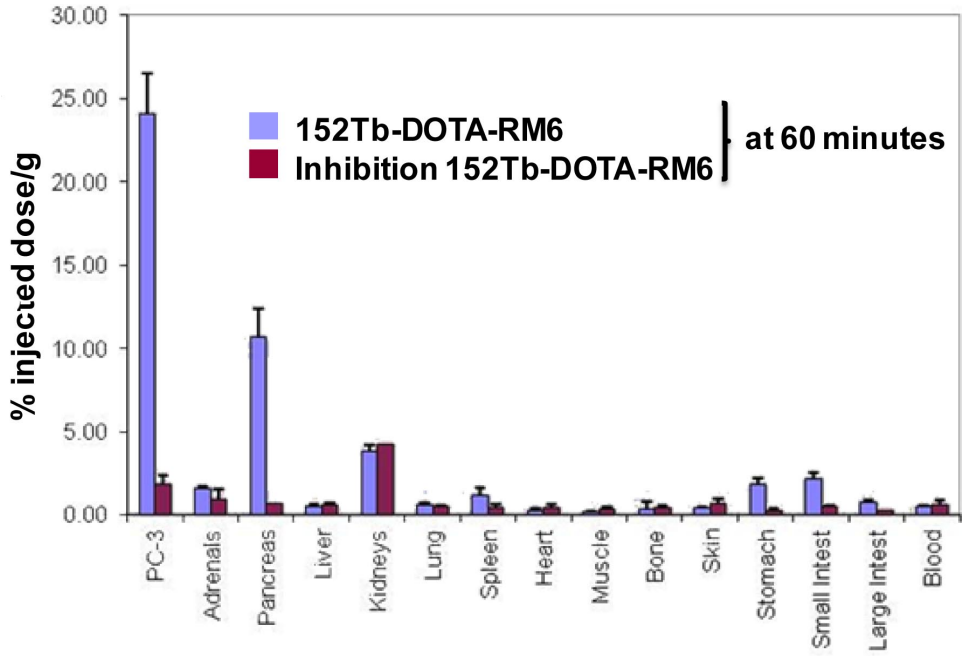


Figure 5. Biodistribution of ^{152}Tb-DOTA-RM6 at 60 minutes post injection in mice baring the prostate PC3 cancer line. A competitive inhibition experiment realised with simultaneous injection of cold radio ligand in excess showed specific tumor uptake. Image courtesy of : [73].

The advanced made at CERN-MEDICIS in collaboration with hospitals and clinics will allow many more applications in the future, especially for the therapy of pathologies with limited treatment modalities, such as unresectable pancreatic cancer.
Many studies already suggested the use of radioactive isotopes for pancreatic cancer treatment as shown through the article review listed below.

4.2 Pancreatic cancer

Pancreatic cancer represents a significant cause of morbidity and mortality, being the 10th leading cause of death worldwide. The overall 5-year survival rate is under 5% for

confirmed ductal adenocarcinoma [75]. Surgery remains the only curative treatment known.
The treatment strategies in locally advanced tumors may depend on whether the disease is resectable, unresectable or borderline resectable.
For localised resectable pancreatic adenocarcinoma, current recommendations include surgical resection followed by 6 months adjuvant therapy. Options are for example Fluoropyrimidine or Gemcitabine with concurrent radiotherapy.

Based on the M.D. Anderson criteria, borderline resectability can be defined as a tumor contact with less than 180 degrees circumference of the superior mesenteric artery, short-segment involvement of the common hepatic artery or short-segment occlusion of the superior mesenteric vein or portal vein that allows surgical reconstruction [76]. In those cases of borderline resectability, surgery is recommended, followed by adjuvant therapy. In locally advanced unresectable disease, where the tumor is in contact with the superior mesenteric artery on more than 180 degrees circumference or when there is another vessel involvement without a feasible surgical reconstruction, neoadjuvant therapy is recommended first [75].

In metastatic disease, current options include for example chemotherapy with Folfirinox or Gemcitabine plus Abraxane [26].

80% of patients present an unresectable disease at diagnosis. Even amongst the patients undergoing surgical resection, 80% will develop local recurrence and/or distant metastases and die within 5 years [77]. Therefore it is necessary to identify new treatment modalities. Many studies have identified new possible targets in the treatment of pancreatic cancer, which might be of interest in particular in locally advanced and/or metastatic disease.

a) Unsealed source therapy for pancreatic cancer treatment

- Targeting neurotensin receptors in pancreatic adenocarcinoma

In pancreatic adenocarcinoma cells, there is an over-expression of neurotensin receptors, which could be targeted by unsealed source therapy [19]. As mentioned above, radiolabelled neurotensin analogs have been successfully tested at CHUV, in collaboration with CERN. In vitro studies showed a high affinity of the ^{68}Ga-labelled

neurotensin analogue (^{68}Ga-DOTA-NT-20.3) for the human pancreatic ductal adenocarcinoma cell line AsPC-1 [78].
A recent study used neurotensin receptor antagonist coupled to ^{177}Lu (^{177}Lu-3BP-227) in 6 patients with metastatic pancreatic adenocarcinoma, showing feasibility, improvement of symptoms and quality of life in all of the patients and even partial response in one of the patients [48].
These studies indicate that radiolabelled neurotensin analogs are a potential new therapeutic option for the treatment of unresectable pancreatic adenocarcinoma, which could benefit from the vast isotope production at CERN-MEDICIS.

- Targeting somatostatin receptors in neuroendocrine pancreatic tumors

The somatostatin receptor is over-expressed on the cell surface of the majority of neuroendocrine tumors and can be used for imaging and targeted treatment when no surgical cure is possible.

DOTA-coupled peptides bound to the positron emitter ^{68}Ga have been developed for somatin receptor scintigraphy, such as DOTATOC, DOTATATE and DOTANOC. They present with higher receptor affinity than Octreotide [20].
These peptides have also been tested for radionuclide therapy on pancreatic neuroendocrine tumors (pNET). A retrospective trial with ^{177}Lu-DOTATATE on metastatic inoperable grade 1 and 2 pNET showed to be effective with a median progression free survival of 24 months and an overall survival of 53 months [79].
There have been a few case reports showing that somatostatin-receptor-targeted therapy could also be used for neoadjuvant therapy to render initially inoperable pNET resectable, using ^{177}Lu-DOTATATE [80] and ^{90}Y-DOTATATE [81]. ^{90}Y is a beta-emitting radionuclide with a radiation path length of 5mm, suitable for bulky tumors such as pancreatic tumors.

Finally, somatostatin-receptor-targeted therapy could also be effective on pancreatic adenocarcinoma as there are somatostatin receptor subtypes which are highly expressed in exocrine pancreas adenocarcinoma. A preclinical study used DOTATOC coupled to the alpha-emitter Bismuth-213 (^{213}Bi) on human pancreatic adenocarcinoma cells. In comparison with the beta- emitter ^{177}Lu-DOTATOC, ^{213}Bi-DOTATOC showed higher relative biological effectiveness and consecutively was more effective in decreasing pancreatic adenocarcinoma cell survival [82].

- Radioimmunotherapy

There have been also a few preclinical and clinical studies of radioimmunotherapy for treatment of pancreatic adenocarcinoma, with radionuclides conjugated to tumor-directed monoclonal antibodies.

The anti-mucin monoclonal antibody PAM4, is highly specific for pancreatic carcinoma and is expressed in more than 85% of pancreatic adenocarcinomas [83]. The antigen to PAM4 is MUC5AC, a secretory mucin expressed *de novo* in early stages of pancreatic neoplasia and throughout disease progression [84].

TF10 is a humanised, PAM4-based, recombinant bispecific monoclonal antibody, which can be radiolabelled and used for pre-targeted radioimmunotherapy [85].
In pre-targeted radioimmunotherapy, the tumor is first pre-targeted with an antibody construct, such as TF10, which has affinity for the tumor-associated antigen and affinity for a radiolabelled hapten which is administered in a later phase [86]. This step-by-step strategy of administering radioimmunotherapy has shown to reduce toxicity. In a pre-targeted radioimmunotherapy study with TF10-^{90}Y-IMP-288, nude mice bearing human pancreatic cancer xenografts were given TF10 and then received a ^{90}Y peptide later, which was as effective as radioimmunotherapy with ^{90}Y-PAM4 but with less toxicity. Combinations with gemcitabine and dose fractionation of the pre-targeted radioimmothrapy enhanced therapeutic responses [83].

Humanised PAM4 (Clivatuzumab) can be conjugated with DOTA and labelled with ^{90}Y to form ^{90}Y-Clivatuzumab, which has been proven to be active in advanced pancreatic cancer in phase I studies [87], combined with low doses of Gemcitabine which is a known radiosensitiser [88].
A phase Ib study of administering fractionated radioimmunotherapy with ^{90}Y-Clivatuzumab in patients with metastatic pancreatic cancer after a median of three prior therapies, appeared to be feasible and safe, with or without Gemcitabine [89]. Cytopenias (especially transient thrombocytopenia) appeared to be the only significant toxicities. A Phase III trial with ^{90}Y-Clivatuzumab and Gemcitabine versus placebo and Gemcitabine in metastatic pancreatic cancer is underway (PANCRIT®-1).

Therefore, different targets for unsealed source therapy in pancreatic cancer have been suggested and proven to be feasible.

b) Brachytherapy for pancreatic cancer treatment

The radioactive isotopes produced by CERN-MEDICIS can also be directly implanted within the tumorous tissue requiring treatment, using brachytherapy. After radioactive seed placement, the target tissue is continuously exposed to radiation, which produces localised tissue injury and high tumor ablation. The tumor volumes and number of implants required must be evaluated before implantation to optimise the treatment. The sealed radiation source can be administered through CT-guided percutaneous implantation, endoscopy or surgery. This method is already used in prostate and breast cancer therapy, through high-dose-rate brachytherapy with ^{192}Iridium implants [90] [91].

Various studies have shown that it could be applied for unresectable pancreatic cancer therapy.

- CT-guided percutaneous implantation

A study on CT-guided percutaneous implantation of ^{125}Iodine seeds directly in pancreatic lesions was performed in patients with stage III and IV pancreatic carcinoma [92]. With its long half-life of 59.7 days, ^{125}I is appropriate for treatment of rapidly growing tumors such as pancreatic cancer.

Implantations were performed with anterior, lateral and posterior approaches, without any significant adverse effects and less toxicity than standard radiotherapy.

Another study with ^{125}I-seeds brachytherapy in patients with unresectable pancreatic cancer (stage III and IV), showed after two months 70% pain relief in patients, an overall response rate (including complete and partial remission) of 65.4% and a local control rate of 88.5% [93].

Finally, a meta-analysis of 23 studies [22] concluded that ^{125}I-seeds brachytherapy as a monotherapy leads to an overall survival of 9 months in patients with advanced pancreatic cancer. When combined with other therapies such as chemotherapy, the overall survival in these patients reaches a duration of 12 months. Brachytherapy with ^{125}I-seeds implantation in combination with cryoablation was found to be associated with the longest survival : up to 14 months.

Cryotherapy is performed by inserting, under local anaesthesia and under guidance of ultrasound or CT, a cryoprobe through the peritoneal or retroperitoneal approach (based on the location of the tumor). It can also be performed on liver metastases using additional cryoprobes which are inserted through the right intercostal space. The cycles

of freezing are performed once all the probes are inserted. ^{125}I seed implantation is often performed following cryoablation. Studies comparing cryosurgery in combination with ^{125}I seed implantation and cryosurgery alone showed higher survival rates and longer median survival in the patients undergoing combination treatment [94][95].

- Brachytherapy through endoscopy

Endoscopic ultrasonography (EUS)-guided brachytherapy has shown to be a feasible and safe treatment of unresectable pancreatic adenocarcinoma using radioactive seeds with isotopes such as Iridium-192 (^{192}Ir), Palladium-103 (^{103}Pd) or the most frequently used Iodine-125 (^{125}I) [96]. EUS-guided brachytherapy has the advantages of accurate positioning, mild injury and a shorter puncture distance than CT-guided percutaneous implantation.

In a recent retrospective clinical study, patients with stage III and IV pancreatic head adenocarcinoma underwent endoscopic brachytherapy through implantation of Iodine-125 seeds [97]. Results showed no serious complications, a partial remission rate of 80% of the patients with stage III disease and an improved quality of life through an improved median *Karnofsky* performance status score.

Another interesting study evaluated the results of EUS-guided brachytherapy combined with intratumoral implants for sustained delivery of 5-Fluorouracil in patients with advanced pancreatic cancer [98]. A mean of 18 Iodine-125 seeds and 36 implants delivering 5-fluorouracil were inserted into the tumors. No local complications or haematologic toxicity occurred. There was a partial response in 1 out of 8 patients, a minimal response in 2 out of 8 patients and a stable disease in 3 out of 8 patients. 50% of the patients presented pain reduction and improved *Karnofsky* performance status score.

- Brachytherapy through minimally invasive surgery

Encapsulated radioactive sources, such as Iodine-125 seeds, can also be placed within the tumor through minimally invasive surgery. The Da Vinci Surgical System available at HUG could enable the surgeon to insert the seeds with great precision, at a safe distance to prevent unwanted irradiation, with minimal damage or complications for the patient. However, few studies have been carried out yet to examine the potential benefits of robotic-assisted brachytherapy. Some studies described brachytherapy through surgery with the Da Vinci System in large animals (pigs) after thoracoscopic wedge resection

[99] and in patients with prostate [24] or bladder [25] cancer. There hasn't been any study using brachytherapy with the Da Vinci System in patients with pancreatic adenocarcinoma so far.

A study was performed in eight patients with unresectable pancreatic head tumors, suffering from pain of high intensity who were candidates for palliative surgery due to jaundice and/or recurrent ileus [100]. They underwent perioperative high dose rate brachytherapy with ^{192}Iridium implants. During the surgery, after palliative choledochoenteroanastomosis and gastrointestinal bypass using a Roux-en-Y loop, a catheter was implanted through the abdominal wall and the transverse mesocolon, to prepare the patients for later brachytherapy. Brachytherapy was initiated at the 6th post-operative day in fractionated doses of 5 Gy, by inserting temporary ^{192}Ir-implants.
The patients who underwent perioperative palliative brachytherapy described pain relief whereas the patients who didn't undergo brachytherapy needed gradual increasing doses of narcotic painkillers. Mean survival time was 6.7 months in the brachytherapy group, versus 4.4 months in the group where no brachytherapy was performed.

Brachytherapy seems to decelerate the tumor growth and decreases the pain associated with the cancer. More studies need to be performed to examine the effect of brachytherapy on survival in patients with pancreatic adenocarcinoma.

Another study examined the combination of palliative surgery through biliary and gastric bypass associated with surgical brachytherapy in patients with unresectable pancreatic head adenocarcinoma [101]. The study was prospective nonradomised. In the group undergoing brachytherapy, during exploratory laparotomy after Kocher manoeuver, needles were implanted into the tumor and spaced at parallel intervals of 10 mm, extending at ≥ 5 mm beyond the margins of the mass. The needles allowed to verify positioning and were retracted if bile, blood or pancreatic juice issued from the needle. ^{125}I seeds were then injected at the location of the needles. A median of 27 seeds per patients were implanted. For radiation protection, surgeons carrying a dosimeter wore lead aprons and gloves.
No mortality occurred in the perioperative period in both groups, with or without brachytherapy and there were no significant differences in morbidity and length of hospital stay. Tumor responses were significantly different : in the group undergoing brachytherapy, partial response rate was 56% versus 0% ($P < 0.001$) and progression

was of 24 versus 85% (P= 0.013). The median survival time was longer as well, corresponding to 11 months in the brachytherapy group versus 7 months. In addition, the patients undergoing brachytherapy described an improved quality of life.

CT-guided, endoscopic or surgical brachytherapy is therefore a valuable option for palliation of symptoms and could be combined with chemotherapy or external beam radiotherapy to improve length of survival and local tumor control.

5. Conclusion

This review of literature highlights the progresses in the field of nuclear medicine for the diagnosis and the treatment of aggressive tumors such as unresectable pancreatic adenocarcinoma. These advances were possible only through collaboration with research facilities such as the CERN-MEDICIS infracture, which provides a variety of radioisotopes with different properties that can be selected for diagnosis and/or therapy. Terbium and Lutetium are two lanthanides of particular interest, with a high theranostic potential.

The CERN-MEDICIS facility produces new isotopes for unsealed internal radiation therapy, by coupling the produced isotopes to tissue-penetrating delivery compounds, as well as new isotopes for brachytherapy. Brachytherapy is feasible through CT or US-guided percutaneous implantation, endoscopic implantation or surgical per-operative implantation of seeds carrying the radioisotopes.

Many studies testing these strategies in patients with unresectable pancreatic adenocarcinoma showed pain reduction and longer survival length. These techniques could be combined to current therapies, such as chemotherapy and external beam therapy, to improve results. Further large-scale studies are necessary and multidisciplinary collaboration is essential for this purpose.

6. Acknowledgements

Firstly, I would like to express my gratitude to my advisor Prof. Léo Bühler for his great help during my thesis and related research, for his patience, motivation and knowledge.

Besides my advisor, I would like to thank Prof. Thierry Stora, who provided an opportunity to visit the MEDICIS facility at CERN, explanations about the different steps of isotope production and related scientific articles.

My sincere thanks also goes to Dr. David Viertl and his team, who procured many insightful ideas and research articles for the writing of the thesis and who gave me access to the research facilities at CHUV, allowing me to see the microPET.

Lastly, I would like to thank my parents for their continuous support during my career and for inspiring me.

Without their precious support the writing of this thesis would not have been possible.

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8. Appendix

Non-exhaustive list of keywords used for the review of the literature :

- alpha radiation
- beta radiation
- brachytherapy
- borderline resectable
- CERN
- CERN-MEDICIS
- chelators
- cryosurgery
- CT-guided
- endoscopy
- gamma radiation
- ion beam therapy
- ISOLDE
- isotope production
- lutetium
- metastates
- neoadjuvant
- neurotensin receptor
- palliative surgery
- pancreatic adenocarcinoma
- pancreatic cancer
- perioperative
- percutaneous
- PET
- radioimmunotherapy
- radioisotopes
- radiotherapy
- somatostatin receptor
- SPECT
- terbium
- theranostics
- unsealed source therapy