Production of pharmaceutical radioisotopes

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Tiivistelmä

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Radioisotooppien tuottaminen
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Pro gradu- tutkielmassani perehdyn radioisotooppituotantoon, sen haasteisiin sekä radiolääkkeiden eri käyttötarkoitusten esittelyyn. Työssä käydään läpi perusedellytyksiä ja käsitteitä radiolääkkeiden turvalliselle ja tarkoituksenmukaiselle käytölle ja tuotannolle.

Radioisotooppeja voidaan tuottaa niin hiukkaskiihdyttimillä kuin ydinreaktoreissakin. Lisäksi tietyillä generaattorimenetelmillä voidaan itse käyttöpaikalla tuottaa lyhytikäisiä isotooppeja, jotka ovat pitkäikäisten isotooppien hajoamistuotteita. Joitain isotooppeja voidaan hyödyntää sellaisenaan, mutta usein niitä tarvitsee jatkojalostaa liittämällä biologisiin tai kemiallisiin yhdisteisiin. Keskeisiä haasteita ja menetelmiä kiihdytintuotannossa käydään läpi tarkemmin fluori-18, jodi-123 ja aktinium-225 isotoopeille.

Avainsanat: Radioisotooppi, radioisotooppituotanto, radioisotoopit, radiolääke, radiolääketuotanto, radionuklidi

Abstract

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This master's thesis talks about radioisotope production, its challenges and the introduction of nuclear medicine purpose of use. Basic principles and concepts for safe and appropriate production and use of radioisotopes are gone through.

Radioisotopes can be produced in particle accelerators and nuclear reactors. Also generator systems can be used at the site of use to produce short lived radionuclides from their parent nuclides. Some isotopes can be used as is, but most need to be attached to other molecules, called vectors. Essential challenges and methods for accelerator production are undergone regarding fluorine-18, iodine-123 and actinium-225 isotopes.

Keywords: radioisotope, radioisotope production, radiomedicine, nuclear medicine, nuclear medicine production, radionuclide

Contents

1 Introduction

Usage of radionuclides in medicine first began quite fast after the discovery of radioactivity at the end of the nineteenth century and in the 1920's radioactive tracer was used for the first time for medical purposes. Discovery of particle accelerators and nuclear reactors increased nuclear medicine applications notably and fast development started after the Second World War. Even though Radioactive substances induce contradictory views because of their hazardous nature, which is remembered especially because of some historical events, their applications in medicine are significant. Nuclear medicine is an established practice in cancer treatment and body function imaging in different fields of medicine. [1]

Nuclear medicine is a medical field where radiating sources of radioactive substance, radiopharmaceutical, is used to diagnose or treat diseases with. Using radiopharmaceuticals one can study changes in organs metabolism and functions. In 1960's the most commonly used radionuclide was iodine-131, but in the year 2000 84 % of examinations in Finland were done using technetium-99m and new nuclides for medical use are investigated. [1]

Radionuclides are produced with nuclear reactors and particle accelerators with varying yields and qualities. The object of this thesis is to study these methods and their differences from the standpoint of the JYFL accelerator laboratory and look into the therapeutical and imaging thecniques done with radioisotopes. The yields depend on a number of things like the production method, target and product nuclide. To see the profitability of radionuclide production in Jyväskylä some suggestive yields of cyclotron production were calculated for actinium-225, iodine-123 and fluorine-18 in chapter 5.4. Chapter 5 as a whole has been done as part of

research training (FYSS9470 Erikoistyö) course.

2 Nuclear physics

2.1 Basic concepts

An atom consists of neutrons, protons and electrons. Neutrons and protons, which are also called nucleons, make up the nucleus. Their amount is given as the mass number A. The atomic number Z is the number of protons in the nucleus and it determines the element. Now the nuclear composition can be presented as an imaginary substance X, with the number of neutrons N, as follows

$$^{\mathrm{A}}_{\mathrm{Z}}\mathrm{X}_{\mathrm{N}}.$$

The elements that have the same amount of protons, but different number of neutrons, are called isotopes. For example $^{127}_{53}\mathrm{I}_{74}$ is a stable isotope of iodine, but $^{126}_{53}\mathrm{I}_{73}$ and $^{128}_{53}\mathrm{I}_{75}$ are radioactive isotopes of iodine. Adding or removing a proton changes an element into another. Nuclei with the same number of neutrons, but different number of protons, are isotones and nuclei with the same mass number A are isobars. Isobars have very similar nuclear properties whereas isotopes have identical chemical properties [2].

Unstable elements, also used in medicine, are called radioisotopes, and more accurately they should be called radionuclides – atoms with unstable nuclei that decay through radioactive disintegration towards a more stable atom. This decay happens so that the unstable parent nucleus emits particles – parts of its own nucleus – or energy in the form of a photon and eventually becomes a stable or unstable daughter nucleus. What emits from the nucleus depends on the nuclear composition of the parent and usually these parents are heavy nuclei, such as molybdenum, iodine or

uranium. [2, 3]

2.2 Decay processes

The decay mode that a nucleus has can be seen from the Chart of Nuclides which is presented in Figure 1. In Figure 1 are all known nuclei in the universe. Black boxes are stable or extremely long lived nuclei and they do not decay or decay very slowly, with lifetime longer than the age of the solar system [2]. Isotopes are horizontally on the same line and isotones vertically on the same line. Most of the elements are radioactive as can be seen from the different colours in the map. The nuclei there above the stable elements are mostly β^+ active (light blue colour) whereas the ones below are β^- active (pink colour). Large part of the heavy nuclides are alpha active (yellow) and also spontaneous fission may occur with some elements. [2, 4, 5]

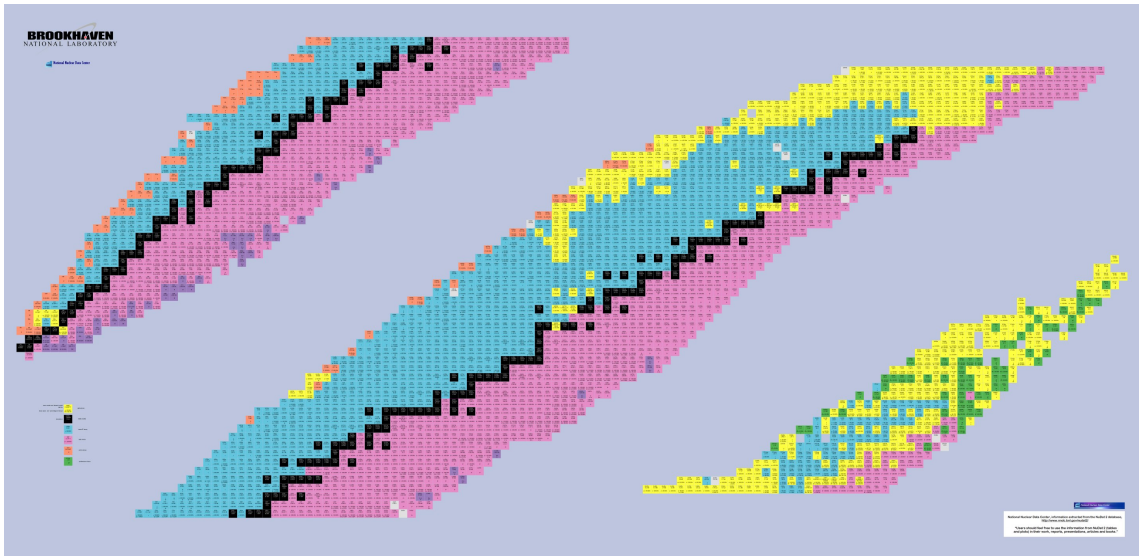

Figure 1. Chart of nuclides. Source: National Nuclear Data Center, information extracted from the NuDat 2 database, http://www.nndc.bnl.gov/nudat2/

Alpha decay occurs usually in heavy elements by emitting an alpha particle, a helium nucleus ${}^4_2\mathrm{He}_2$. For example alpha decaying uranium-235 produces thorium-231 and

an α-particle as follows:

$$^{235}_{92}\mathrm{U}_{143} \rightarrow {}^{231}_{90}\mathrm{Th}_{141} + {}^{4}_{2}\mathrm{He}_{2}$$

Here both proton and neutron numbers are decreased by two. Thus the daughter nucleus has a mass number $A - 4$, because of the exiting of the helium-4 nucleus.

Beta-plus decay gives out positrons (or anti-electrons) e^+ that result from supernumerary proton transformation to a neutron, electron neutrino ν_e and a positron. This happens in elements that are proton rich, elements that have a large Z compared to N.

$$\beta^+ : p \rightarrow n + e^+ + \nu_e$$

The exiting positron will soon after emitting collide with an electron of the surrounding material. These two will then annihilate and change into two 511 keV energy photons, that leave in exactly opposite directions. By detecting multiple of these annihilations their collision position can be calculated, and used in imaging, commonly called positron emission tomography, PET. The resulting nucleus will have the same mass number A, but one less proton (Z-1) and one more neutron (N+1) [6].

A competing decay to β^+ is electron capture. Here the nucleus captures an atomic electron from its orbit, combines it with a proton forming a neutron and emits a neutrino. This results in an unstable, excited daughter atom with $Z - 1$.

$$EC : p + e \rightarrow n + \nu_e$$

The electron leaves a vacancy in the electron cloud which is filled by a electron from a higher energy orbit. This releases energy in the form of an X-ray or it can be transferred to another electron which then is ejected from the atom. The latter is called an Auger electron.

Beta-minus is opposite to beta-plus decay and it results from neutron transformation to a proton, electron and an antineutrino $\bar{\nu}_e$.

$$\beta^- : n \rightarrow p + e^- + \bar{\nu}_e$$

This happens in neutron rich elements, where the amount of neutrons compared to protons is too high. The daughter nucleus will have the same mass number A, but one more proton (Z+1) and one less neutron (N-1).

Gamma decay occurs when an excited state transits to a lower level of energy. Gamma rays are not particles but energy called photons and the amount of energy they possess depends on their origin: the difference of the energy level of the excited state and the end state. An example of this is when the daughter nucleus resulting e.g. from beta decay may go to an excited state that is referred to as a metastable state. When this state is released, the nucleus emits a gamma photon and the nucleus will go to its ground state. The energy of the gamma photon is then the energy between the metastable and the stable state. Gamma decay does not change the composition of the nucleus, thus the parent and daughter are the same chemical element. [2, 4, 5]

Internal conversion is a competing decay process with gamma decay: instead of emitting a photon, de-exitation happens by knocking one electron out of the atom. Again the element stays the same, like in gamma decay, but the hole in the electron shell is filled by a higher energy electron, resulting in X-ray or Auger electron emission.[2, 4, 5]

Nucleon emission can happen in highly excited proton or neutron-rich elements and for very heavy elements also spontaneous fission can occur in which a nucleus breaks into two or sometimes three lighter nuclei usually leading also to beta particle, gamma ray and neutron emissions. [2, 4, 5]

2.3 Types of radiation

By definition radiation is transfer of energy by electromagnetic waves or particles and it can be either ionizing or non-ionizing. Ionizing radiation are X rays, γ rays, energetic neutrons, protons, electrons and heavier charged particles [7].

In addition ionizing radiation is either directly ionizing or indirectly ionizing. Directly ionizing particles are fast, charged particles, whereas indirectly ionizing particles are uncharged such as gamma photons or neutrons. The energy of the directly ionizing particle is deposited straight in the medium through different interactions, mostly Coulomb interaction, because the charge interacts with the orbital electrons inside the medium, while indirect ionization happens so that the neutral particle creates a charged particle in the medium. This newly created charged particle affects in similar manner in the medium as the directly ionizing one. [7, 6]

Gamma rays, ultraviolet photons and X rays are indirectly ionizing radiation, because as said earlier, they are uncharged "particles". Gamma rays are short in wave length and of very different energies. They originate from excessive energy in the nucleus, and are released, when the excited nucleus translates into a more stable state. Because they penetrate matter very well, due to their short wave length, they are a good imaging tool.[6]

Radiation origins from nature and man-made sources. Most of our annual dosage comes from nature, and mostly from radon, which is a noble gas rising from the ground as a product of the uranium decay chain. The unit of radiation dosage is a sievert (Sv). [8]

2.4 Half-life and Activity

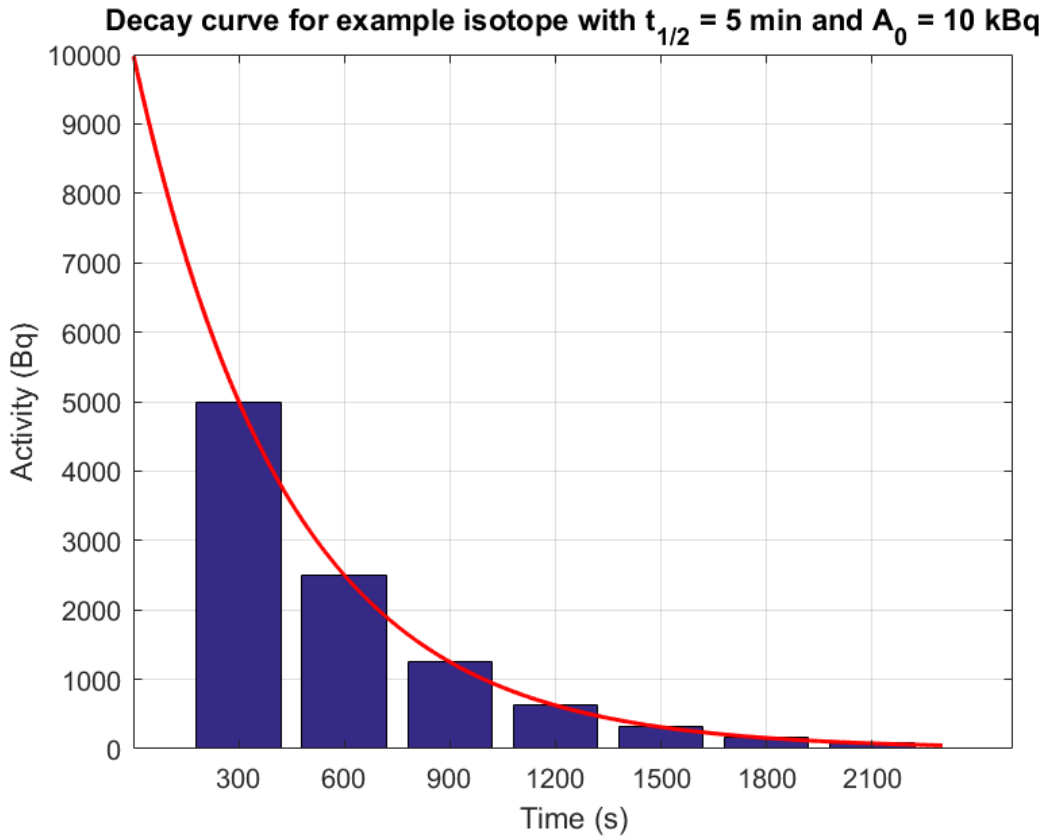

Figure 2. The decay of an example isotope with half-live of 5 minutes and starting activity at 10 kBq shows the exponential decay of activity as a function of time. The red curve is the decay curve which is generated using the Equation 4 and the bars represent the activity at times where another half-life has passed. The figure was plotted using MATLAB 2016b.

Activity A is the number of decays in a unit of time and its unit is becquerel [Bq], which is decays per second. Activity is equal to the change in the number of radioactive atoms dN in a short time dt [2, 4, 5]:

$$A = \frac{dN}{dt} = -\lambda N. \tag{1}$$

λ is the decay constant. λ is characteristic to each isotope and is a well defined probability of decaying per unit of time. The minus sign is for the activity and the

amount of decaying nuclei decrease with time. Solution to this equation is called the radioactive decay law:

$$N(t) = N(0)e^{-\lambda t}, \tag{2}$$

where $N(0)$ is the number of atoms at time $t = 0$ and $N(t)$ the number of atoms of the same isotope at time t [2, 4, 5].

A radioisotope is an unstable isotope that decays with time to another stable or unstable element. The time, that this decay takes, measured with half-life $t_{1/2}$ in which the radioisotope's amount is cut down to half from the original. It can vary from milliseconds to billions of years [2]. Half-live is defined as follows from the derivation of the decay law:

$$t_{1/2} = \frac{ln(2)}{\lambda} = \frac{0,693}{\lambda}. \tag{3}$$

Since decay is an inverted exponential function of time, also the amount of radioactive material decreases exponentially with time. This is shown in Figure 2 , where it can be seen that after seven half-lives there is almost no activity left.

Activity of a nuclide is of the same form as Equation 2 it can be derived from

$$A(t) = A(0)e^{-\lambda t} = |\frac{dN}{dt}|, \tag{4}$$

where A(t) is the activity at time t and A(0) in the beginning at $t = 0$ [1]. The activity depends on the radionuclide, its half-life and quantity.

When the daughter nucleus of a decay is also radioactive, sequential decays will occur. The parent and daughter nuclei decay together with different parameters. The parent A decays as follows

$$\frac{dN_{\mathrm{A}}}{dt} = -\lambda_{\mathrm{A}} N_{\mathrm{A}}, \tag{5}$$

and the daughter B does in similar manner, but the decay of the parent A increases the amount of nuclei B, which leads to

$$\frac{dN_{\mathrm{B}}}{dt} = -\lambda_{\mathrm{B}} N_{\mathrm{B}} + \lambda_{\mathrm{A}} N_{\mathrm{A}}. \tag{6}$$

The amount of nucleus B created in time t is then

$$N_{\mathrm{B}}(t) = N_{\mathrm{B}}(0)e^{-\lambda_{\mathrm{B}}t} + \frac{\lambda_{\mathrm{A}}}{\lambda_{\mathrm{B}} - \lambda_{\mathrm{A}}} N_{\mathrm{A}}(0)(e^{-\lambda_{\mathrm{A}}t} - e^{-\lambda_{\mathrm{B}}t}). \tag{7}$$

The Equation 7 is especially useful for systems where the daughter nucleus B is generated from the parent nucleus A. These generator systems are discussed more in chapter 4.2. [2, 4, 5]

2.5 Reaction Cross Section and Yield

Cross-section is a measure the relative probability of the occurrence of the reaction [4, 2]. Let's consider a thin target b and beam a, which is a flux of monoenergetic particles distributed over an area S. The beam hits the target and creates products c and d. The reaction can be seen like [2]

$$a + b \rightarrow c + d.$$

Now let n_a be number of particles in the beam (a), hitting the target (b) in a unit of time, while N_b is the number of particles in a unit area of the target (b). Similarly n_c and n_d are the number of particles c and d produced in a unit of time. The cross-section, σ, is the ratio of the products and the starting material. The products c and d are produced in equal amounts, thus the reaction cross-section can be defined with equation [2, 4, 5]

$$\sigma = \frac{n_c}{n_a N_b} = \frac{n_d}{n_a N_b}. \tag{8}$$

In a another way cross-section can be expressed as

$$\sigma = \frac{\text{event rate per nucleus}}{\text{incident flux}}. \tag{9}$$

Generally the total cross section of a reaction is defined as

$$\sigma_{tot} = \frac{n_1 + n_2 + n_3 + \ldots + n_m}{n_a N_b} = \frac{\sum n_i}{n_a N_b} \tag{10}$$

for a bombarding particle a, which hits the target b and creates a variety of products $n_1, n_2, n_3, \ldots, n_m$. Thus partial cross section can be defined for the i-th particle by

equation [2]

$$\sigma_i = \frac{n_i}{n_a N_b}, \tag{11}$$

so that the total cross section can be stated in the form

$$\sigma_{tot} = \sum \sigma_i. \tag{12}$$

Since all particles in the beam have the same speed v_a, the flux Φ is given

$$\Phi = \rho_a v_a \tag{13}$$

where ρ_a is the density of the beam, in other words flux is the number of particles (in the beam) in a volume hitting the target per unit time. Beam intensity is therefor

$$I = \Phi S, \tag{14}$$

as in particles per unit time, where S is the cross sectional area of the beam [5]. Reaction rate R is

$$R = N_b \sigma \Phi = N_b \sigma \frac{I}{S} \tag{15}$$

when N_b particles in the target are exposed to the beam. The rate doesn't depend on the direction of the incident particles and therefor the flux can be defined as the total path length in a unit volume in a unit time for all the particles. Because of that the reaction rate can be defined in terms of beam intensity I and target thickness t by equation

$$R = N_b \sigma \frac{I}{S} = I \sigma n_b t, \tag{16}$$

where n_b is the number of the target atoms per unit volume [5]. n_b for an atom with mass M_b, in atomic mass units, and density ρ_b is

$$n_b = \rho_b \frac{N_A}{M_b},$$

where N_A is the Avogadro's constant. Now using this information, the reaction rate in equation 16 becomes

$$R = I \sigma \rho_b \frac{N_A}{M_b} t. \tag{17}$$

Reaction cross section has the dimension of area per nucleus. If we consider a detector detecting the products, the area of the detector is small and defines a solid angle $\mathrm{d}\Omega$. The detector observes a fraction of all the outgoing particles at different polar angles at rate $\mathrm{d}R_{\mathrm{out}}(\theta, \phi)$.

$$\mathrm{d}R(\theta, \phi) = \frac{\mathrm{d}\sigma}{\mathrm{d}\Omega} N \Phi \mathrm{d}\Omega. \tag{18}$$

Differential cross section is the constant of proportionality, $\frac{\mathrm{d}\sigma}{\mathrm{d}\Omega}$. Cross section can be solved through integration of equation 18 over angles θ and ϕ

$$\sigma = \int \sigma(\theta, \phi) \mathrm{d}\Omega. \tag{19}$$

Cross section is usually denoted in units of barn and one barn is $10^{-28}\mathrm{m}^2$, which is the approximate geometric cross sectional area of a nucleus of mass number $A = 100$ [5].

Nuclear reactions take place while the target is bombarded and the number of arising nuclei can be determined as a function of bombardment time. In most situations, since the amount of nuclei converted is very small compared to the total amount of target nuclei, the rate of production P can be considered as independent of time [2, 4, 5]. The rate in which the amount of radioactive nuclei increases is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = P - \lambda N. \tag{20}$$

If P is a constant, equation 20 can be solved to the form of

$$N(t) = \frac{P}{\lambda}(1 - e^{-\lambda \cdot t_{irr}}). \tag{21}$$

The initial rate of increase of for the build up of N is P at $t = 0$. This can be seen looking at equation 20, because $N(t = 0)$ is zero. After multiple half-lives the increase saturates as N approaches equilibrium (P/λ), which can be seen looking at equation 20 is when $\mathrm{d}N/\mathrm{d}t = 0$. [5]

Activity is of the product is defined as

$$A(t) = \lambda N(t) = P(1 - e^{-\lambda \cdot t_{irr}}), \tag{22}$$

where λ is the decay constant of the product, P is the production rate and t_{irr} is the irradiation time. Production rate P is given by on of the reaction rate equations 15, 16 or 17. The activity at the end of bombardment looks similar

$$A_{EOB} = A_{sat} \cdot (1 - e^{-\frac{ln(2) \cdot t_{irr}}{T_{1/2}}}) \cdot I = A_{sat} \cdot (1 - e^{-\lambda \cdot t_{irr}}) \cdot I, \tag{23}$$

where the $(1 - e^{-\lambda \cdot t_{irr}})$ term is called the Build-up factor and I is the beam current [4, 5, 2] [A. Virtanen, private conversation]. Using this information the equation above can be simplified to

$$A_{EOB} = A_{sat} \cdot B \cdot I. \tag{24}$$

2.6 Attenuation of radiation

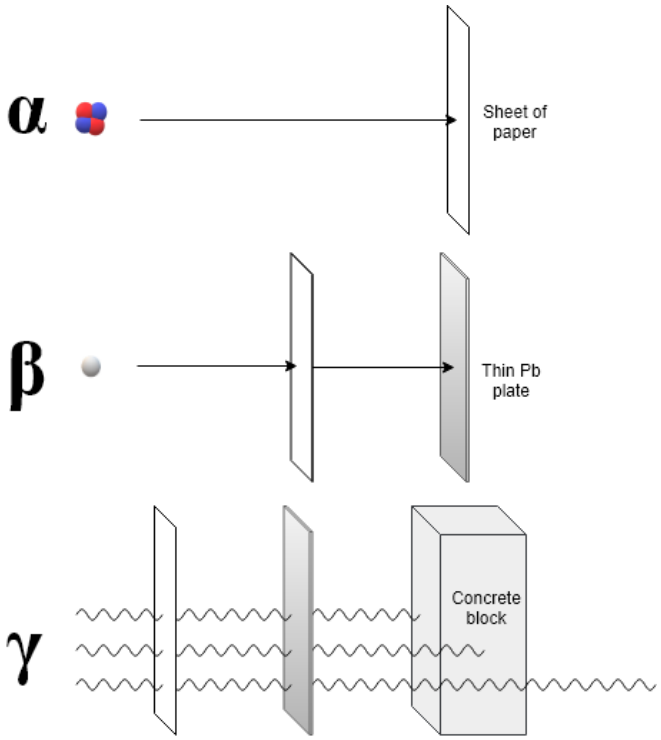

Figure 3. Demonstration of the attenuation of α, β and γ radiation: alpha particles are stopped by a sheet of paper, beta stops at a thin lead plate and gamma can penetrate even a thick concrete block.

Photons typically have from zero to a few interactions in matter and they attenuate

exponentially, whereas the attenuation of electrons and other charged particles varies a lot depending on matter. Photon interactions are described with cross-sections and they have attenuation co-efficients, while charged particles have a range depending on the material stopping powers.[9]

Attenuation of radiation depends on material and radiation type and its energy: α particle stops to a paper, whereas gamma photon continues in the material until it disappears with some probability by undergoing a photoelectric effect, Compton scattering or pair production. Attenuation is demonstrated in Figure 3. This effect happens because charged particles, thanks to electrical force between them and nuclei of the absorber, interact much more likely with matter than photons. Thus charged particle range in matter is shorter than the penetration of photons and their interactions with matter are referred to as non-penetrating radiation.[9, 7]

Range is the distance a particle travels through the absorber before it stops. The isotopes emitting gamma radiation can be used for nuclear imaging rather than the treatment, because they don't stop basically at all in the human body. This allows the gamma photons to be detected outside patients body and the fuction they are used to image can be reconstructed with computers. Attenuation coefficient tells a materials efficiency to attenuate a photon.[9, 7]

For a thin target of a homogeneous material of thickness dx, that is bombarded with a beam of photons, there is a probability for an interaction of an individual photon with the target material:

$$\mu dx = N_a \sigma dx, \tag{25}$$

where N_a is the number of atoms in a unit volume, σ is the total interaction cross section per atom and μ is the linear attenuation coefficient [9]. Attenuation can be seen in decrease of intensity I of the photon beam. The absorber of thickness dx reduces the intensity by dI. In this way it can be said that

$$\frac{\mathrm{d}I(x)}{\mathrm{d}x} = -\mu I(x). \tag{26}$$

Minus sign in the equation 26 is for the decreasing intensity I with increasing thickness x of the absorber. Integrating over equation 26 results in equation

$$I(x) = I(0)e^{-\mu x}. \tag{27}$$

μ is always a property of the absorber, or attenuator. By dividing with $I(0)$, the equation can be expressed in form

$$\frac{I(x)}{I(0)} = \frac{I_{out}}{I_{in}} = e^{-\mu x}, \tag{28}$$

where $I(0)$ is the intensity before the target and $I(x)$ is the intensity coming out of the target. The linear attenuation coefficient μ is dependent on the medium and the energy of the photons hitting it. The denser the medium, thus the larger the atomic number Z on the medium, the greater the attenuation [10]. For scattering atoms the linear attenuation coefficient can be calculated by equation:

$$\mu = N_a\sigma = \frac{1000N_A\rho}{A_r}\sigma, \tag{29}$$

where N_A is the Avogadro constant, A_r is the atomic weight of the attenuator medium and ρ its density. The dimensions of μ are thus m^{-1} [9].

Mass attenuation coefficient is the linear attenuation coefficient divided by the density of the absorber. It's unit can be for example cm^2/gram. The difference between absorption and attenuation is that absorption is energy transfer from the beam to the matter and attenuation describes the weakening of the beam. Linear attenuation coefficient is dependent of density and therefore also the physical state of the attenuator material. Mass attenuation coefficient doesn't depend on density of the absorber and is thus more suitable for data compilations [9].

Charged particle interactions with matter are different photon interactions because of the strong electrical interaction between the atoms of the medium and the charged particle. The strong interaction is caused by the Coulomb force, which results in the particle transferring its energy to the medium in a short distance. The equation for Coulomb force is

$$F = \frac{1}{4\pi\epsilon_0}\frac{|q_1||q_2|}{r^2} \tag{30}$$

where ϵ_0 is the permittivity constant, q is the particle charge times unit charge and r is the distance between these two charges [11, 7].

From the Coulomb force can be seen that the force between an alpha particle and a nucleus is twice as large as the force would be with a beta particle with the same distance r. This is due to the $+2$ charge in the helium nucleus, which is twice as much as the ± 1 charge of a beta particle. By interacting with the medium the charged particle can cause excitation or ionization in the atom. In the excitation the kinetic energy of the incident particle is partly transferred to the electrons of the medium. Usually the energy is enough to make an electron go from an inner shell to an outer shell of the atom. After excitation the electron returns to the lower shell releasing the excess energy as an x-ray. The x-ray released is a characteristic x-ray, which is characteristic to the element. Ionization happens if the incident particle is energetic and the energy is sufficient to eject an electron from the atom making it an positive ion. Ionization can be caused by photons as well. [10, 7]

LET (linear energy transfer) is the amount of energy transferred in a given distance by a particle moving through an absorber [10]. It is the linear rate at which radiation is absorbed in the medium. Secondary electrons are created by the primary particle or photon, because it transfers its energy to the electrons knocking them out of their electron shells. The linear energy transfer is defined as [7]

$$\frac{\mathrm{d}E}{\mathrm{d}l} = \frac{\text{Average energy imparted in the medium by a charged particle}}{\text{distance}}. \tag{31}$$

Unit of LET is usually kiloelectronvolts per micrometer [10] and some examples of LET values can be seen in Table 1.

As can be seen from Table 1, the average energy deposited to the medium is 12.3 with 1 keV energy electrons whereas its 2.3 with 10 keV electrons. The problem with the concept of LET is that it can vary dramatically in the microscopic level and it peaks at the end of the particle range. The changes in LET while the particle travels through matter leads to poor correlation of average LET with the macroscopic biological effects. [7]

Table 1. Linear energy transfer values for some radiation types [7, p. 58]

Radiation type	LET $\frac{\text{keV}}{\mu\text{m}}$
10 MeV proton	4.7
2.5 MeV α-particle	166
1 keV electron	12.3
10 keV electron	2.3
1 MeV electron	0.25

3 Nuclear Medicine

3.1 Medicinal therapy using radiation

Goal of radiotherapy is to give a lethal dose of radiation to a tumour without giving excess dosage to surrounding healthy tissue. The lethal effect of radiation originates from its ionizing ability. The incident radiation ionizes the atoms in tissue molecules in a timescale of 10^{-16} s or less. These ionized molecules attend in chemical reactions creating free radicals or excited molecules. Free radicals may then attach to biological structures altering their biological functions, which may come apparent in a timescale from hours to years. The lethal radiation dose can be given by methods of either external or internal therapy in which this thesis focuses on. [4, 12]

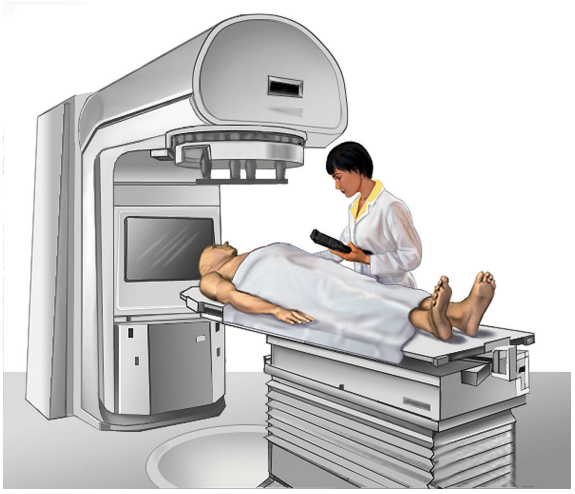

Figure 4. External radiotherapy machine source: National Cancer Institute, Creator: NIH Medical Arts (2007); https://visualsonline.cancer.gov/details.cfm?imageid=9413 (copied: 25.08.2018)

External radiotherapy is carried out with accelerators, such as linacs, betatrons or mircotrons. X rays are used, besides diagnostics, in radiation oncology. Most of modern radiotherapy is carried out with linear accelerators or teletherapy machines, which use gamma ray sources, mostly 60-Co contained in a cylindrical steel capsule. [12]

Ion beam radiotherapy has the advantage of energy depositing, that can be concentrated on a narrow few millimeter region at an adjustable depth inside the tissue. Heavy ions such as carbon can reach millimeter precision in principle anywhere in the body. Deposit of the ion beam energy increases with penetration depth until it reaches a peak, which is called the Bragg peak, at the end of its range. [13]

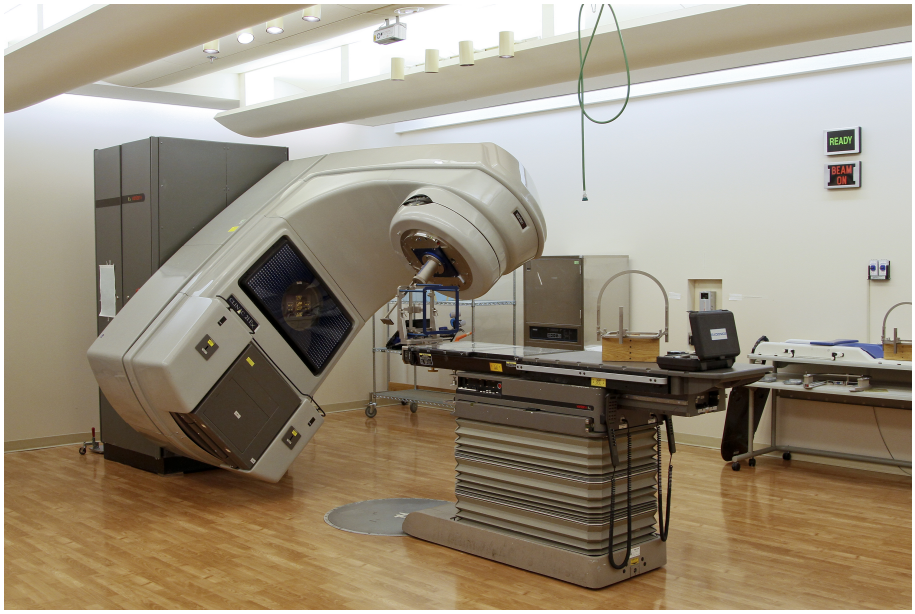

Figure 5. A linear accelerator or LINACs can be used both in radionuclide production and external radiation therapy. This figure presents a patient being prepared for external therapy with a LINAC. National Cancer Institute, Creator: Daniel Sone (Photographer) 2010; https://visualsonline.cancer.gov/details.cfm?imageid=8755 (copied: 25.08.2018)

3.1.1 Therapy with Radionuclides

Radionuclides are often synthesized with chemical substances or compounds that help the nuclide to reach the organ or tissue under treatment or imaging. Together they are called radiomedicine. In general, radiomedicine is injected to the patient, but in some cases they can also be ingested or inhaled. There are different ways for a medicine to accumulate to their destination.[1]

The nuclide used should have an appropriate radiation dose deposition, so that it gives high local dose to the tumour, but no dose to surrounding healthy tissue. This determines the type of radiation of the nuclide, but other factors like half-life, maximum energy, range and therefore relative biological effectiveness need to be considered. [1, 14]

Some nuclides travel to certain organs, like iodine to the thyroid gland on their own, but often the nuclide needs to be attached to a pharmacological or biological substance. Chemically the radioisotope can be for example as a salt, like sodium iodide with radioactive iodine. Radionuclides attached to an organic molecule, such as an antibody, are called vectors. [1, 14]

Most common radionuclides in radiomedicine are beta emitters. They provide a wide spectrum of energies and ranges, and many options for radionuclides suitable for radiotherapy. If measured in millimeters, the range of a beta particle in soft tissue is approximately five times its maximum energy in MeV's [14]. High energy beta particles are therefore better for large tumour treatment, since otherwise, with small volume tumours, most of the dose would be deposited in tissues around the tumour. Pure beta emitters provide a high local dose, which makes them more ideal for therapy, but a nuclide emitting both beta and gamma may be used simultaneously in imaging. The latter though also increases the overall dose of the patient without any therapeutic benefit. [1, 14]

Most commonly used radionuclide in nuclear medicine is 131-I, but it isn't the ideal one by its properties. Its decay is a relatively low energy beta, but two-thirds of its decays result in medium or high energy gamma emissions. This means it would be useful in small tumour treatment, but it will give a significant radiation dose to the surrounding tissues. Gamma emissions are useful in imaging but they don't give a proper therapeutic effect since they attenuate poorly in tissue. [1, 14]

For internal radiotherapy β^-, α, Auger electron and X-ray decaying emitters could be used and the simplest way to use them is brachytherapy – mechanically take the isotope to the tumour site. Usually it is done by putting a wire of β^- emitting ^{192}Ir, a X-ray emitting stent of either ^{125}I or ^{103}Pd, or the latter as a seed. The radioisotope is left in to the tumour and after a time period, removed. In palliative therapy pure β^- emitters like ^{32}P($T_{1/2} = 14.3d$), ^{169}Er ($T_{1/2} = 9.4d$) and ^{90}Y ($T_{1/2} = 2.7d$) are introduced as gels, glass microspheres or conglomerates into joints and cavities. [15]

Tumour cells originate from normal cells, but they can be distinguished from each other by malignancy induced changes on the cell surface. Tumour associated antigens can be recognized by antibodies, which can be used as carriers for radionuclides. This field of nuclear medicine is called radioimmunotherapy in which an antibody is used as a vehicle delivering the radionuclide. The radiolabelled antibody (radioimmunoconjugate, RIC) spreads through out the body and is cleared up from normal tissues due to metabolism. Thanks to the antigen-antibody interaction, the radioimmunoconjugate accumulates and remains at the tumour site in a prolonged manner which allows the therapy to be efficient. [14]

Usually the isotopes in radioimmunotherapy are combined with a bioconjugate with high affinity and selectivity. The bioconjugate is more likely to attach itself to a certain cancer cells that are overexpressing cell membrane proteins called antigens. Depending in the bioconjugate this type of therapy is called Peptide Receptor Radio Therapy (PRRT) with peptides as conjugate or radioimmunotherapy with antibodies as conjugate. Antibody-fragments, nanoparticles, microparticles etc. can also be

used as bioconjugates. [16]

Injecting too much of the bioconjugate may lead to saturation of of the binding sites. Saturation would lead to decrease in conjugate selectivity thus it is important to have a radioisotope with high specific activity to minimize the injection of unnecessarily large amount of the therapeutic agent. The uptake of bioconjugates to the tumour vary substantially from patient to patient, which is why a personal dosimetry is required so that the amount of activity can be adapted accordingly. [16]

Maximum range for alpha particles is of less than $0,1\,\mathrm{mm}$[14] which is about the diameter of a few cells. Alpha particles are very high LET making them good biological effectiveness, but because of the very short range, the particle would basically need to be attached to the target cell to be effective. Their mass is large so they can be very toxic compared to beta particles especially when internalized by the target cell. Alpha active radioisotopes are therefore good candidates for tumour specific radioimmunotherapy or alpha therapy, in which the α-RIC is taken to the cancerous cell. There it can cause the most damage to the malignant tissue stunting the growth of cancer. [14]

Auger electrons could work in similar manner as alphaimmunotherapy. Auger electrons have a short range of $0.1 - 5\,\mu\mathrm{m}$ [14] thus they are only effective when very close to the cell nucleus. The relative biological effectiveness of this type of isotope is increased by cellular internalization. There are many diagnostic radionuclides that decay by EC, like 99m-Tc, 125-I, 123-I, but they don't give high local doses because they disperse in the body. 111-In and 125-I are the most widely investigated radioisotopes of this type, but this is still an area of research. [14]

Normal tissue has a very well formed vascular system, but one characteristic of cancerous growth is loss of cell behavior and function control. Tumour blood vessels do not form and mature properly and are disorganized. This causes implications considering radioimmunotherapy, since it limits the delivery of radioimmunoconjugate

and reduces oxygen concentration therefore also reducing the effect of the therapy. Large bulky tumours are harder to access through the vascular system thus small metastases may be the best targets for radioimmunotherapy [14].

Ideally a targeting antibody would retain only in the tumour tissue through interaction with the tumour membrane-associated molecules – target antigens. Target antigens are uniquely or overly expressed by the target cells, which allows the antibody to trace its target efficiently. [14]

Affinity is one of the most important features for an antibody [14]. It tells how strong the binding between antibody and antigen is and defines how well the antibody will localize to the tumour. Binding happens through non-covalent bonds between the amino-acids on the antigen surface and binding site of the antibody. There is contradictory evidence of increasing affinity by modifying antibody binding site – in-vivo it has been either beneficial or no effect on tumour localization. There might also be a threshold above which affinity no longer increases tumour localization or other factors become limiting. [14]

3.2 Nuclear imaging

The basic method for nuclear imaging is to give the patient an intravenous radiomedicine that accumulates to a tumor or an organ. This accumulation is followed using a gamma camera by taking pictures around the area from different directions and angles. It can also be used to track the radionuclide entering and exiting from the organ under examination or even during surgery. [1]

The basic principle of the gamma camera is that a gamma photon exiting the organ is detected by a detector, but before that the emitted radiation is collimated to form a picture. A collimator blocks part of the incoming radiation so that the received signal is more specific, because the radiation from the organ goes to every possible direction. This way the information is more specific, because it narrows down the

incoming flux. Though a collimator degrades the resolution with distance, thus it is important to have a specific collimator for a specific purpose such as high or low energy high resolution collimator. [13]

A collimator defines the lines of response (LOR's) and it functions as a mechanical lens. It blocks gammas that are not aligned with the LOR's. This means that it blocks all other photons but the ones that are traveling directly along the axis of the apertures of the collimator. A collimator is made of a dense material with thousands of long and narrow apertures in it. The material has a high atomic number and it's typically lead. The apertures are parallel to the LOR's and the idea is that one LOR corresponds one point in the object that is imaged. In reality this would mean that only a few gammas get to the detector, but on the other hand enlarging diameter of the holes result in degraded resolution. Photons that aren't aligned with the LOR's are absorbed by the septa that is in between the holes as can be seen in figure 6. [7, 3]

Using a collimator with large holes will result in more detected photons, which in turn makes the resolution worse than with small holes. But another thing to consider is noise: in these images it results from statistical variations in the number of photons in a given time interval. Noise is described by Poisson statistics and the coefficient of variation is inversely proportional to the square root of the number of counts detected. This means that the more counts one gets, the less disturbing noise is in the image. Thus, enhancing resolution results in bigger, but not disturbing noise level of the nuclear image and the other way around. One can optimize the image by choosing a collimator suitable to channel photons of the wanted energy. That way the image can be influenced depending on the imaging agenda and one can choose to focus to enhance either imaging speed or imaging quality, or magnify or minify the image [3]. In figure6 are two different types of collimators, where it can be seen how the hole size effects the path of the photons. [7, 3]

After collimation the gammas are detected typically by scintillating detectors. Scin-

tillation crystal in the detector converts the incident gamma ray into a visible light photon. Optimal crystal is made of dense high Z material which tends to stop all hitting γ's completely so that no signal is lost. Crystal thickness also affects the resolution and sensitivity. The thicker it is the more sensitive it is, but the resolution is lower since the gammas can be absorbed farther inside the crystal. In that case the light photon emerges far from the point where the gamma hits the crystal making the resolution lower. Photomultipliers multiply the photons so that they can be detected by photocathode of the detectors which convert the light photons into an electric signal that is amplified and formed into an image by computers. [3]

A gammacamera is used to image gamma rays emitted by any radioisotope, but the same working principle is used in other imaging techniques. In positron emission tomography (PET) scanning (Figure 7) the used radiomedicine is a positron emitter that is combined to a molecule –together they are called a radiopharmaceutical. The tracer is injected to a patient, which is then placed into a PET scanner and the radionuclide is naturally emitting positrons all the time during this procedure. In the target (tissue, organ or blood circulation) immediately after the positron is emitted, it encounters an electron. Since they are of opposite charge, they will collide and annihilate sending out two 511 keV gamma photons going in exactly opposite directions and they are detected by using coincidence detection technique. Three dimensional distribution of the radioactive nuclide can be reconstructed by detecting multiple of these coincident photons in similar manner to the gamma camera, but with multiple detectors. In only few minutes a whole body scan can be performed using PET, which represents the distribution of the tracer that reflects physiological uptake or metabolism. Using for example fluoro-deoxyglucose, glucose metabolism as a biological process can be observed. Common isotopes used as radiopharmaceuticals for PET are ^{18}F, ^{11}C, ^{68}Ga, ^{82}Rb. [13]

Single photon emission computed tomography (SPECT) is based on a gamma emitting source. Like the name says single gamma rays are detected without any coincidence condition, and using projection from different angles 3D distribution of the

radioisotope can be reconstructed. The camera head or heads can rotate around the patient to acquire multiple images for cross sectional views of the section of interest. Common nuclides used for SPECT are ^{99m}Tc, ^{153}Sm, ^{123}I,^{131}I, ^{111}In, ^{90}Y. [13]

Thus the biggest difference in SPECT and PET is that in SPECT there is only one gamma ray that is detected and in PET the positron annihilates with an electron and creates two gammas of 511keV going in opposite directions. Interpreting of PET and SPECT images alone is difficult because they don't show much of the anatomical structures unlike anatomical imaging techniques. Combining CT or MRI images to PET and SPECT images solve that problem. CT and MRI, are used to localize the PET- and SPECT images more accurately in the body of the patient. [3]

X-ray Computed Tomography (CT) is based on data acquisition of X-ray attenuation in the section of interest that is then reconstructed to a digital image of the section. It works basically like regular X-ray imaging, but multiple images are taken from all around the section of interest to form a three dimensional reconstruction. Modern day clinical CT scanners are able to produce images of about 0.3 mm resolution and slice thickness of 0.5 mm. Drawback in CT scanning is that it increases radiation dosage.[13]

3.3 Restrictions for radionuclides used in medicine

When considering radioisotopes used as medicine, their half-life is an extremely important factor: one does not want to expose a human body to excess radiation. Too much of it will do more harm than good, which is why the isotope used in a procedure is chosen carefully. The isotope needs to be stable enough to be taken to the place of treatment, but also decay fast enough not to give the patient too much dosage. [6]

Besides the half-life of a radionuclide, also what type of radiation it emits and at what energy, is important for the treatment of the patient. Very few nuclides emit

only one type of radiation, and actually most of them are emitters of two radiation types, most commonly β^- and γ.[6]

Besides their half-life and the time radioisotopes or vectors are present in the human body, also production, transporting, waste treatment must be taken into account. Small amount of all the radionuclides fill these requirements and all of them are artificially made using cyclotrons or nuclear reactors.

Range is an important factor, since the particles must go deep enough but not too deep in the tissue. Irradiation might be incomplete if the range is too small, and if it is too big, healthy tissue surrounding the tumour will be irradiated with consequent damage. High LET particles will cause more damage and are therefore more toxic than low LET particles, because their energy is deposited through a shorter length in tissue.Nonetheless, the high LET emission will require a more homogeneous distribution through out the tumour in order to be efficacious therapy. Mixture of isotopes might increase the homogeneity of the energy distribution of the emissions, thus increasing efficiency. [17]

Larger tumours might be better to be treated with isotopes with energetic emissions, since with longer range those can reach further in the tissue. Also, providing the cross-fire effect, more energetic emission compared to the RIC, they might reach areas that the RIC cannot. [14]

Ideal nuclide would have a half-life that is short enough to give sufficient dose, but not more than that. Half-life of a radionuclide should be $1.5 - 3.0$ times the tumour peak uptake time. There are indications from mathematical modelling that longer lived isotopes may have some advantage. [14]

Pharmacokinetics of the antibody and appropriate choice of radionuclide are critical in order to optimize therapy. Radioactivity will increase in the body until it reaches a peak and starts to decrease thanks to biological and physical half-life of the radiolabelled antibody [14, p. 21]. Uptake extent and duration are influenced

by clearance of the antibody from blood, tumour accessibility, antibody properties, stability of the labelling and target antigens half-life on the tumour membrane. [14]

There is evidence of an inverse relationship between tumour size and the dose delivered by radioimmunotherapy, which would indicate that best targets for RIT are micrometastases distributed around the body that other treatments can not reach. [14]

Absorbed dose is the energy of ionizing radiation absorbed by any material. Its SI unit is gray (Gy), which is equal to 1 joule absorbed per kilogram of tissue. Dose equivalent is given by absorbed dose times the weighting factor W_R of the type of radiation. [9]

Most of the radiation damage is considered to happen in the cell DNA, which can be caused by a single hit causing a double strand break or to coincidental interactions making two single strand breaks and thus causing cell death. In external beam therapy a dose is given at high rate (e.g. 360cGy/min and a total of 2Gy) in a short period whereas in RIT, the dose rate is very low for a longer period of time [14]. The damage caused to the cell is related to the linear energy transfer (LET), which is the energy deposited per unit length by radiation. High LET is provided by alpha and beta particles, and electrons or X-rays from internal conversion or electron capture. [14]

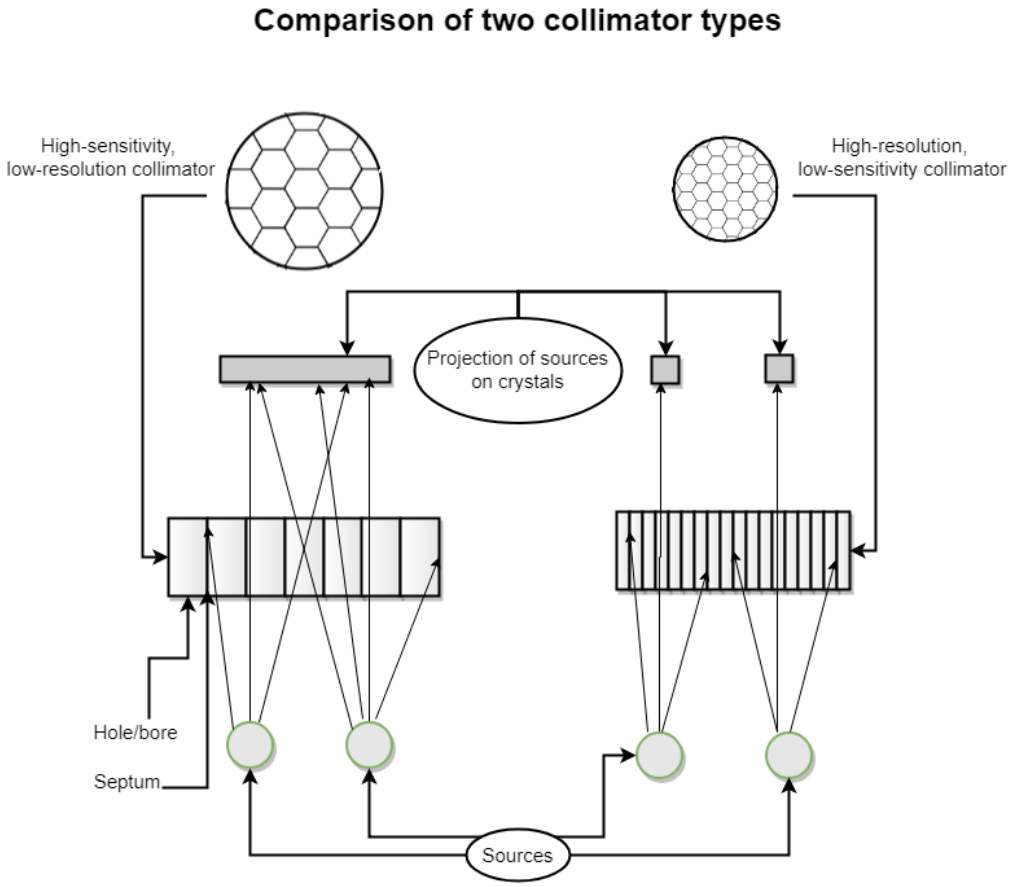

Figure 6. Comparison of two different type of collimators shows how the hole diameter effects resolution and sensitivity. The collimator on the left hand side clearly lets more photons through while the one on the right hand side stops most of the incident gammas and lets through only the ones coming in line with the bores.

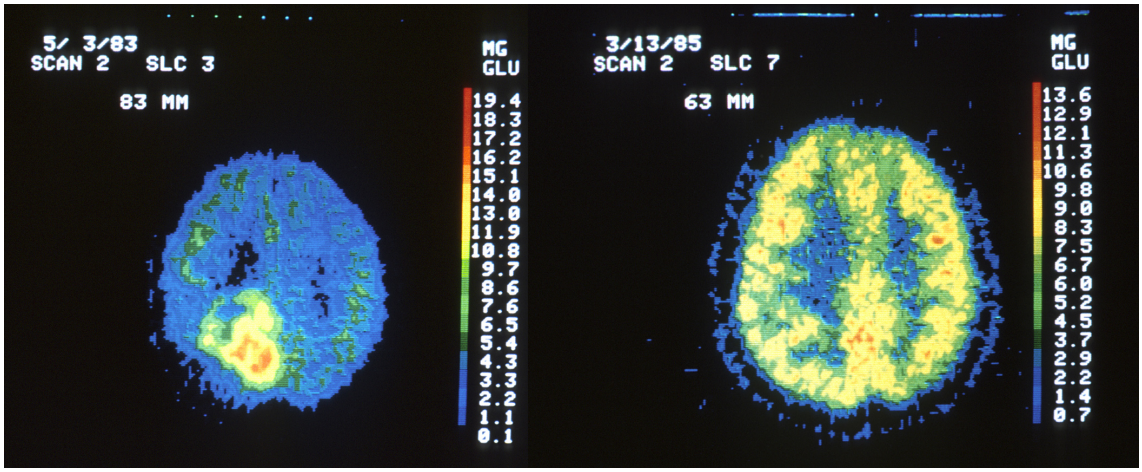

Figure 7. Position emission tomography (PET) of cerebral glucose utilization in a normal individual. This tomogram is through the upper part of the cerebral hemisphere. Note discrimination between gray matter (yellow-red color) and white matter (green-blue color) which uses less glucose. Copyrights: Dr. Giovanni Dichiro, Neuroimaging Section, National Institute of Neurological Disorders and Stroke (copied: 25.08.2018 https://visualsonline.cancer.gov/details.cfm?imageid=1753)

4 Production of radioisotopes

4.1 Use of radioisotopes for medicine

There are multiple ways of generating radioisotopes for pharmaceutical industry. Mostly this is done by nuclear reactors, but also particle accelerators are used. Radioisotopes that are used in molecular nuclear medicine require to have a high specific activity. High specific activity means that in the end product is no other chemically similar element or other isotopes the same element. Basic medical isotope production ways are nuclear reactions generated by cyclotrons with high intensity beams and neutron induced reactions in nuclear reactors. Worldwide there are about 400 research reactors and around 500 cyclotrons, from which most are used at least partly on medical radionuclide production. [15, 18]

The wanted elements are chemically separated from their parents used as targets for the nuclear reactions. Therapeutic radionuclides are often chosen by availability rather than the best decay characteristics for a certain disease [19]. Some examples of radionuclides and their production methods are given in Table 2.

Qaim divides medical radionuclides into four groups according to their functions: soft β^- emitters, γ emitters for SPECT, Positron emitters for PET and radionuclides for internal therapy [15].

There are many gamma emitters which have found application in gamma camera imaging, but in SPECT imaging the radioisotope needs to emit only one gamma photon or one predominant gamma ray within $100-200$keV. This narrows the choice down to five nuclides: ^{67}Ga ($T_{1/2} = 3.26$d), ^{99m}Tc($T_{1/2} = 6.0$h), ^{111}In ($T_{1/2} = 2.8$d),

Table 2. Some radionuclides and their production methods [1, p. 223]

Production method	Nuclide
Cyclotron	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{57}Co, ^{67}Ga, ^{111}In, ^{123}I, ^{201}Tl
Reactor	^{51}Cr,^{75}Se, ^{58}Co, ^{59}Fe, ^{125}I, ^{131}I
Fission products	^{90}Y, ^{131}I, ^{133}Xe
Generators	^{99}Mo/^{99m}Tc

^{123}I($T_{1/2}$ = 13.2h) and ^{201}Tl($T_{1/2}$ = 3.06d), from which ^{99m}Tc is most commonly used. ^{99m}Tc is made by ^{99}Mo/^{99m}Tc generator system, which are more discussed in section 4.2.[15]

4.2 Generators

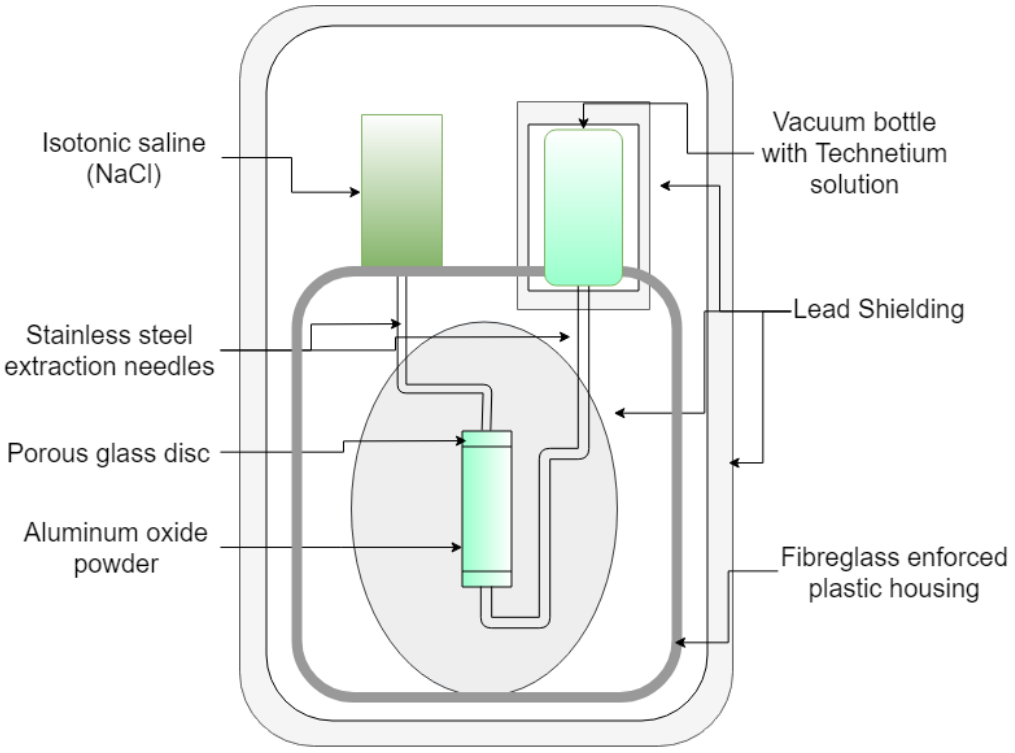

Figure 8. Technetium generator system simplified

Radionuclide generators are composed of nuclides that have parent nuclides with

a relatively long half-lives. They are not used directly, but their faster decaying daughter nuclide is collected. The basic working principle of a generator is that works like a cow: a daughter nuclide is milked from a parent nuclide by eluting the daughter in to a solvent that only the daughter dissolves into. The daughter nuclide needs to be easily separable. [1]

The primary isotope, the parent, is loaded into a generator system and the daughter isotope is grown in to it. The extraction of the final isotope is done by chromatographic techniques, distillation or phase partitioning. The generator can not be loaded with the parent to the maximum – there is a limit, after which also the primary isotope might be eluted. This would lead to contamination of the final product and it could not be used because of the long lived isotope in it. [16]

Most common generator is ^{99}Mo/^{99m}Tc in which ^{99}Mo is the parent and ^{99m}Tc the daughter. An Al2O3-column is filled with ^{99}Mo and ^{99m}Tc is removed from it by elution with saline. The parent nuclide is produced in a reactor by either reaction ^{98}Mo(n, γ)^{99}Mo or ^{235}U(n, f)^{99}Mo. A simplified presentation of a Technetium generator is presented in figure 8. [1]

Technetium-99m decays through isomeric transition emitting 141 keV gamma photon to Technetium-99, which is basically, in radiopharmaceutical point of view, stable with a half-life of $2.1 \cdot 10^5$ years. From the SPECT radionuclides it causes least radiation dose and is almost always available in a clinic via the generator system. [1]

Other generators are for example ^{82}Sr/^{82}Rb, which is used in cardiac perfusion imaging and ^{81}Rb/^{81m}Kr, which is used in lung ventilation scans. Daughter nuclide half-lives are 75 and 13 seconds respectively. ^{229}Th/^{225}Ac generators are used for production of the alpha decaying actinium nuclide production. [1, 15]

4.3 Production with accelerator

Particle accelerator in general has two basic demands, which are that the particle accelerated must be charged and there must be an electric field to accelerate it. There are two main classes of accelerators regarding the way the electric field is produced: electrostatic and cyclic. Electrostatic accelerators have a constant electric field through a voltage difference. The energy of the particle depends on the potential energy difference from the voltage drop inside the accelerator. Example of a electrostatic accelerators are X ray tubes and neutron generators. [12]

Cyclic accelerators are non-conservative and have a magnetic field that causes the particle to follow a path where it is gradually accelerated. The acceleration happens by submitting the particle to a small electrical potential difference multiple times giving it more potential energy on little by little. Cyclotrons, linacs, microtrons and betatrons for example are cyclic accelerators. [12] Linear accelerators produce high energy beams with 4 to 20 million volt energy. Modern linacs are able to reach precision of 2-3% [20].

Accelerator produced radionuclides are mainly made via reactions such as $(\mathrm{p}, x\mathrm{n})$ and (p,α). High specific activity demands that the final product and target are different in their chemical properties to be separated from each other. This means that the Z has to be changed in the process. Beam energies for such reactions are in the range of 10-30 MeV with beam currents of 0.1 to 1 mA [16]. Radioisotopes can be produced with a linear accelerator as well as a cyclotron, the latter one is though more common. Cyclotron produced isotopes are generally neutron deficient and thus decay by electron capture or β^+ emissions, which makes them good diagnostic tools. Positron emitters can only be produced by cyclotrons and some examples of them and their applications in medicine are presented in Table3. [15, 16]

The working principle of a cyclotron (Figure 9) is that the beam of particles is accelerated gradually starting from the middle of the cyclotron. The particles start

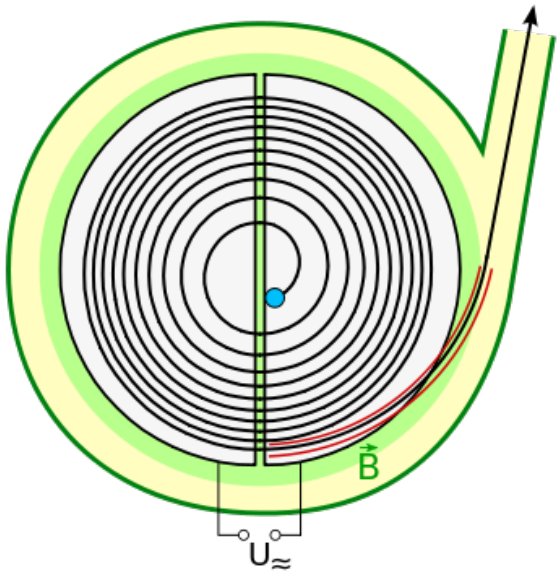

Figure 9. Example of a cyclotron cross section. B is the magnetic field inside the Dees and U is the electric potential difference between the Dees. The magnetic field turns and keeps the charged particle in a circular motion while the electric potential accelerates it. (Figure from Wikipedia: Zyklotron 11.8.2018)

going in a circular trajectory which enlarges at every round because of the electric field accelerating them and magnetic field steering them. After the particles have reached the wanted energy, they will be guided out of the cyclotron to the beam line. The basic idea of cyclotron production is that a target is bombarded with accelerated particles. The nuclear reactions induced by the energetic particle hitting the target give rise to new, different elements. The target atoms are changed into other elements.

Production of ^{123}I has three commonly used methods: ^{123}Te(p, n)^{123}I; ^{124}Xe(p, 2n)^{123}Cs $\rightarrow$ ^{123}Xe and ^{124}Xe(p, pn)^{123}Xe; ^{127}I(p, 5n)^{123}Xe $\rightarrow$ ^{123}I. Iodine produced by these methods is in a suitable chemical form labelling of organic compounds through substitution reactions. [15]

Small cyclotron with energy of less that 20MeV in the energy range of $10-14,5$ MeV can be used for reaction ^{123}Te(p, n)^{123}I. The yield is low though. Medium sized

cyclotron of energy around 30 MeV is used with highly enriched ^{124}Xe gas as target over the optimum energy range $23 - 29$MeV. This is treated more in chapter 5.2. [15]

^{201}Tl is mainly produced through reaction^{203}Tl(p, 3n)^{201}Pb $\rightarrow$ ^{201}Tl using medium sized cyclotron utilizing energy range of $20 - 28$MeV. The precursor ^{201}Pb is separated and let decay for 32 hours. The product it isolated from it as ^{201}TlCl. Thallium as target is toxic, but the product is in a no-carrier-added form and thus is safe. Thalliums trivalent form is medically ineffective so it is useful only in its monovalent form. [15]

^{67}Ga and ^{111}In are produced in a medium-sized cyclotron at an energy range of $18 - 25$MeV via reactions ^{68}Zn(p, 2n)^{67}Ga and ^{112}Cd(p, 2n)^{111}In. These two are used in SPECT, but are considered for Auger therapy [15].

There are a large number of positron emitters, but mostly for routine PET investigations low-energy cyclotron produced ^{11}C ($T_{1/2} = 20.4\,\text{min}$) or ^{18}F ($T_{1/2} = 110\,\text{min}$) are used, and to a lesser extent ^{15}O ($T_{1/2} = 2\,\text{min}$) and ^{13}N ($T_{1/2} = 10\,\text{min}$). Fluorine-18 is transported to medical centers that have PET scanners, but the others are usually used at the production site. ^{68}Ga ($T_{1/2} = 67.6\,\text{min}$) and ^{82}Rb($T_{1/2} = 1.3\,\text{min}$) are also positron emitters used in diagnostics and are produced via generators, but their parent ^{68}Ge ($T_{1/2} = 271$d) and ^{82}Sr ($T_{1/2} = 25.3$d) nuclides are cyclotron produced. The reactions for production can be found in table 6 in chapter 4.5.[15]

^{103}Pd was originally produced via reaction ^{102}Pd$(n, \gamma)^{103}$Pd in a nuclear reactor, but its yield and specific activity could not be improved. Now it is done by cyclotron via ^{103}Rh(p, n)-reaction and ^{103}Rh(d, 2n)-process is also of interest. ^{103}Pd is commonly used for treatment of prostate cancer.[15]

^{211}At is made via reaction ^{209}Bi$(\alpha, 2n)^{211}$At, which needs a very accurate energy range control to avoid formation of ^{210}At, because it decays to ^{210}Po which has a long half-life of 138,4 days. Astatine is separated chemically from bismuth. α

decaying radioiosotopes and alpha therapy are further discussed in chapter 5.[15]

^{67}Cu is useful for SPECT β^- active, with a gamma photon emission. Both reactors and accelerators have been studied for production, but the most effective production route seems to be ^{68}Zn(p,2p)^{67}Cu with proton energy of more than 70MeV. In this reaction also large amounts of ^{64}Cu ($T_{1/2}$ = 12.7 h) and ^{67}Ga ($T_{1/2}$ = 78.3 h) are co-produced. [19]

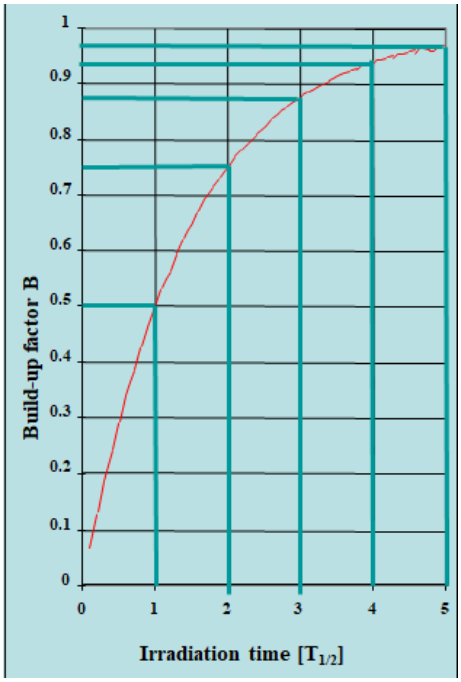

Figure 10. Build-up factor as a function of irradiation time in $T_{1/2}$'s shows how the half-life of a nuclide effects the production of the nuclide.

An important feature in the production isotope production process is the build-up factor B. It comes from the activity equation 23 shown also below:

$$A_{EOB} = A_{sat} \cdot (1 - e^{-\frac{ln(2) \cdot t_{irr}}{T_{1/2}}}) \cdot I = A_{sat} \cdot B \cdot I.$$

Figure 10 presents the build up factor as a function of half-lives. The maximum of the build up is 100 % or $B = 1$, which is the point where the curve is totally saturated. The maximum yield is limited by the saturation activity A_{sat} which depends on the properties of the target. The maximum yield cannot exceed the saturation activity via accelerator production.

Optimum shape for a target has been studied by Howard and Starovoitova in 2014. Motivation for their study was to find more efficient way of producing radionuclides with a linear accelerator compared to reactors. Reactors produce larger amounts of waste compared to accelerators and operate at lower cost. To increase the yield of isotopes with LINACS such as ^{67}Cu, ^{99}Mo, and ^{225}Ac, it is best done by optimizing mass and geometry of the target. [21]

Target system production capacity is a function of the incident beam current and energy. The beam particles hitting and slowing down in the target produce waste heat, which need to be removed from the system to sustain its operation. Talking about water targets like in the production of fluorine-18, the beam may create vapor voids if the thermal capacity is exceeded. This can lead to the beam particles fully pass through the target medium and getting absorbed by the target body. Radionuclides are therefore not produced and in addition the target itself can be damaged because of the high beam current. Removal of excess heat can thus increase the production capacity. [22]

Regarding target materials: silver has a high thermal conductivity which helps cooling the target, it is easy to manufacture and it doesn't react with oxygen easily - these reasons have made it a common commercial water target material. Tantalum has been considered as a replacement for silver because of its inertness and caused lower dose rate than silver due to target activation. Tantalum also produces a better quality fluoride ion, unlike aluminum which traps the fluorine, but it is expensive, its hard to mold and has a low thermal conductivity. Aluminum though is low cost, easy to work on and has better thermal conductivity compared to tantalum, which makes it a good test target. [22]

According to Peeples et al. target performance and optimization for range-thick, such as the ^{18}O water target, targets can be reduced to a heat transfer problem. Models where turbulent boiling through out the target is assumed, experimental results are in a good agreement with the models. It has lead to a conclusion that

a cylindrical target chamber is more efficient in volume compared to the racetrack-shaped conventional cross-section. The model used by Peeples et al. is experimentally proven to predict the targets thermal performance, which has led to fundamental changes in the target designing and to new type of targets, with enhanced production capabilities. [22]

Table 3. Positron emitters for nuclear medicine produced using cyclotrons [15, p. 640]

Nuclide	$T_{1/2}$	Production route	Application
^{11}C	20.4 min	^{14}N(p,α)	PET
^{13}N	9.9 min	^{16}O(p,α)	PET
^{15}O	122 s	^{15}N(p,n)	PET
^{18}F	109.8 min	^{18}O(p,n)	PET
^{38}K	7.6 min	^{35}Cl(α,n)	Cardiology
^{55}Co	17.6 h	^{58}Ni(p,α),^{54}Fe(d,n)	Tumour imaging; Neuronal Ca marker
^{64}Cu	12.7 h	^{64}Ni(p,n)	Radioimmunotherapy
^{66}Ga	9.4 h	^{66}Zn(p,n)	Quantification of SPECT-pharmaceuticals
^{72}As	26.0 h	$^{\text{nat}}$Ge(p,xn)	Tumour imaging; immuno-PET
^{73}Se	7.1 h	^{75}As$(p,3n)$	Selenopharmaceuticals
^{76}Br	16.0 h	^{76}Se(p,n)	Radioimmunotherapy
^{86}Y	14.7 h	^{86}Sr(p,n)	Therapy planning
^{89}Zr	78.4 h	^{89}Y(p,n)	Immuno-PET
^{94m}Tc	52 min	^{94}Mo(p,n)	Quantification of SPECT-pharmaceuticals
^{120}I	1.3 h	^{120}Te(p,n)	Iodopharmaceuticals
^{124}I	4.18 d	^{124}Te(p,n)	Tumour targeting; dosimetry

From technical point of view there has been a lot of development regarding production of short-lived positron emitters for example chemical processing and high-current targetry, like high-pressure gas targets have been developed.[15]

4.4 Photonuclear and photoexcitation reactions in isotope production

Photonuclear reaction has two stages: 1. photon absorbtion 2. de-excitation. Below 10 MeV energy there is narrow resonance peak that corresponds the energy of exciting a single energy level of the nucleus. In the range from 10 to 30 MeV there is a very broad resonance maximum called giant dipole resonance (GDR), which is the region suitable for photonuclear reactions. The GDR represents the total vibration of the neutrons against the protons. Going over 30 MeV in photon energy will cause a neutron-proton pair to interact with it instead of the excitation of all the nucleons. In the second stage the energy absorbed by the nucleus in the first stage is released by emission of a photon, neutron or a charged particle. [23]

Nuclear medicine production via photonuclear reactions has been investigated by Habs and Köster- In their research they studied the $(\gamma, x\mathrm{n} + y\mathrm{p})$ photonuclear and (γ, γ') photoexcitation reactions with γ beams from Compton back-scattering of laser light from relativistic electron beams. γ beam induced photonuclear reactions allow high specific activity production of isotopes like ^{44}Ti, ^{47}Sc, ^{67}Cu, ^{103}Pb, ^{117m}Sn, ^{169}Er, ^{195m}Pt and ^{225}Ac. This type of production would allow more economical production and higher specific activity of nuclides than by classical accelerator or reactor production. Some examples of radionuclides and their half-lives produced via photonuclear reactions and their medical applications are listed in Tables 4 and 5. [16]

γ facility used in Habs' and Kösters study consists of an electron linac which creates a electron beam from which the intense laser beams are Compton back-scattered. An illustration of this type of facility is in figure 11. The facility has two sites for gamma beam production, a neutron time of flight spectrometer and a crystal spectrometer. Electrons are accelerated in the superconducting cavity and decelerated after one loop (in red). [16]

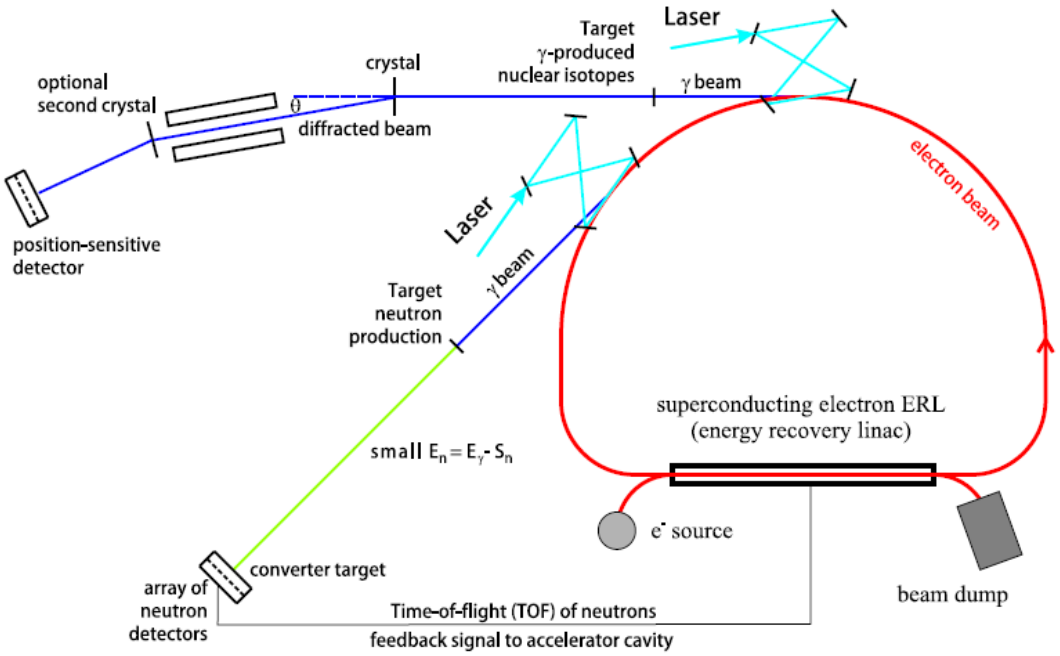

Figure 11. Superconducting Energy Recovery Linac electron beam facility has two gamma production sites, a TOF spectrometer for γ energy monitoring and a crystal spectrometer. [16]

Two isotopes that can be produced via photonuclear (γ, γ') reactions are ^{195m}Pt and ^{117m}Sm. Platinum compounds are cytotoxic and are used in chemotherapy. ^{195m}Pt can be used in SPECT or gamma cameras thanks to its 99 keV gamma ray, but it also emits low energy conversion electrons and Auger electrons. In higher activities ^{195m}Pt could be used for both chemo- and radionuclidetherapy. Neutron capture on ^{194}Pt allows a very limited amount of specific activity to be produced (HFIR, Oak Ridge 0.04 GBq/mg), but the (γ, γ') might produce up to 70 GBq/mg about 20 GBq activity per day. In the photonuclear case the purity would be excellent, since no other long lived isotopes would be produced. [16]

^{117m}Sm can be used for pain palliation in bone metastases. The production rate for ^{117m}Sm is poor in reactors, in high flux reactor specific activities from 0.2 to 0.4 GBq/mg are achived via inelastic neutron scattering. Via (γ, γ') reaction around 0.6 GBq are produced per day with specific activity of 7 GBq/mg using 6 MeV gamma

beams. [16]

(γ, n) reaction is based on a fact that a nucleus will lose a neutron if it is excited beyond the neutron binding energy. Competing reactions are unlikely to cause de-excitation of the energy deposited. In photoneutron production the emission of a single nucleon is dominating in the total cross section of the giant dipole resonance region. Coulomb barrier decreases the emission of charged particles in larger than medium size nuclei. Photoneutron reaction produces a high yield but a low specific activity. Essentially the parent and daughter nuclide are of the same element so to increase the specific activity, they need to be separated for example by nuclear kinematic recoil method which Starovoitova et al. suggest. [23, 16]

Table 4. Medical isotopes produced by photoneutron reactions and some of their medical applications [23].

Nuclide	$T_{1/2}$	Production	Application
^{18}F	110 min	^{19}F (γ, n)	Radiotracer for brain studies, PET
^{47}Sc	3.35 d	^{48}Ca (γ, n)	Bone cancer pain relief, cancer RIT
^{64}Cu	12.7 h	^{65}Cu (γ, n)	SPECT, blood flow studies, colorectal cancer therapy
^{67}Ga	78.3 h	^{69}Ga $(\gamma, 2n)$	Imaging abdominal infections, detect lymphoma and osteomyelitis; evaluate granulomaous diseases
^{75}Se	120 d	^{76}Se (γ, n)	Radiotracer in brain studies, adrenal cortex imaging hyperactive parathyroid gland detection
^{77}Br	57 h	^{79}Br $(\gamma, 2n)$	Label radiosentizers, monoclonal antibody labeling
^{99}Mo	66 h	^{100}Mo(γ, n)	Parent for Tc-99m generator used for brain, liver, lungs, heart imaging
^{131}Ba/^{131}Cs	11.5 d(9.7 d)	^{132}Ba(γ, n)	Intracavity implants for radiotherapy
^{225}Ra/^{225}Ac	10 d	^{226}Ra(γ, n)	Monoclonal antibody attachment for RIT, Bi-213 generator

In photoproton reactions the incident photon is absorbed by the nucleus and an the energy is released by an emission a of proton. When the Coulomb barrier is overcome by the photon energy the photoproton cross-section increases quickly. The advantage of (γ, p) reactions is that the parent and daughter isotopes are different elements, which makes their separation often trivial. Some examples of medical isotopes, which can be produced by photoproton reactions are in table 5. [23]

Starovoitova et al. studied the possibility of photonuclear production of ^{67}Cu and

^{99}Mo. Monte Carlo simulations were used in their study to predict the activity produced via $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo}$ reaction – 1 gram target irradiated for 10 hours with 10 kW electron linear accelerator would lead to production of 700 MBq activity. Separation of ^{99}Mo from ^{100}Mo could be done by either via kinematic recoil method or low specific activity column. ^{67}Cu activity was predicted to be around $1\frac{\text{MBq}}{\text{gkWh}}$ produced via $^{68}\text{Zn}(\gamma, p)^{67}\text{Cu}$ reaction, which mean that, depending on LINAC power hundreds of MBq could be produced daily. Experimental data retrieved from Idaho Accelerator Center were consistent with the theoretical activities with both Copper and Molybdenum. [23]

Table 5. Medical isotopes produced by photoproton reactions and some their medical applications [23].

Nuclide	$T_{1/2}$	Production	Application
^{43}K	22.2 h	$^{44}\text{Ca}(\gamma, p)$	Myocardium imaging
^{47}Sc	3.35 d	$^{48}\text{Ti}(\gamma, p)$	Bone cancer pain relief, cancer RIT
^{57}Co	271 d	$^{58}\text{Ni}(\gamma, p)$	Radiolabeling agent for vitamin B12 deficiency and Schilling's test
^{67}Cu	62 h	$^{68}\text{Zn}(\gamma, p)$	Cancer diagnostics and RIT, planar imaging, SPECT
^{90}Y	64 h	$^{91}\text{Zr}(\gamma, p)$	Implants, radioembolization
^{111}In	2.8 d	$^{112}\text{Sn}(\gamma, p)$	Radiolabeling Leukocytes, bloodscans
^{131}Ba	11.5 d	$^{131}\text{Ba}(\gamma, p)$	Intracavity implants for radiotherapy
^{166}Ho	26.8 h	$^{167}\text{Er}(\gamma, p)$	Treatment of rheumatoid arthritis, cancer RIT
^{177}Lu	6.71 d	$^{178}\text{Hf}(\gamma, p)$	Restenosis treatment, RIT

4.5 Production with reactor

One of the most common nuclear reactions to make radioisotopes is neutron capture (n, γ), which transforms a stable element to its own radioactive isotope. If the cross section of the reaction is high and a target is irradiated with high neutron flux density, high specific activities can be made. Neutron energy in these reactions can vary from thermal to epithermal energies (meV to keV), which are provided by high-flux reactors. Important to know is that the produced specific activity depends on the neutron flux density ($\frac{n}{\mathrm{cm^2 s}}$) and not the total number of neutrons. Irradiation reactors are optimized to keep total neutron rate, and thus the thermal power, relatively low and provide the high flux in a limited volume. [16]

Nuclear research reactors can be roughly divided into to two classes: swimming pool or tank-in-pool and tank type reactors. The pool type reactor has a core immersed in an open pool of water, which acts as a cooling ant, moderator and radiation shield. The core is reachable from the top of pool, which allows loading and unloading targets easily with simple devices. Inside the core cadmium can be used as control rods to absorb neutrons which lessens the reactivity of the core. Beryllium and graphite on the other hand may be added as neutron reflectors in the core as plates for example. The reactor cooling happens in larger reactors by forced coolant flow, which is now water, and heat exchangers or convection induced by the hot core. The fuel itself is inside a separate aluminum or zirkonium alloy to prevent its proliferation. [24]

The (n, γ) reaction doesn't make the final product directly, but a precursor that β decays to the final product. This makes it possible to chemically separate the bulk from the remaining target material, because they are different by their chemical properties. Reactor production in most cases leads to neutron excess radionuclides and they are mostly β^- active. [15] [16].

From the soft β^- emitters some of the most important nuclides are ^{3}H ($T_{1/2}$ =

12.3 a), ^{14}C($T_{1/2}$ = 5730 a) and ^{125}I ($T_{1/2}$ = 59.4 d), which are all produced by nuclear reactor. Tritium is produced by ^{6}Li(n, α)-reaction on Li or LiF target and is usually available as gas or tritiated water. ^{14}C is produced by (Al)^{14}N(n,p)^{14}C-reaction and usually available as $^{14}CO_2$ or Ba$^{14}CO_3$. ^{125}I is available as $^{125}I^-$ by irradiating natural or enriched Xenon-124 in an Al-capsule. [15]

Also as soft beta emitters ^{33}P ($T_{1/2}$ = 25.3d) and ^{35}S ($T_{1/2}$ = 87.5d) have limited applications regarding *in vitro* investigations and are both produced in a high fast flux nuclear reactor in a non-carrier added form. Producing ^{33}P is done by reaction ^{33}S$(n, p)^{33}$P, where ^{33}S is isotopically enriched. Reaction for ^{35}S production is K^{35}Cl(n, p)^{35}S. [15]

^{32}S$(n, p)^{32}$P and ^{89}Y(n, p)^{89}Sr reactions produce ^{32}P and ^{89}Sr with high specific activity, but with rather low cross sections and yields. ^{89}Sr is produced in Dimitrovgard, Russia at RIAR, a high fast flux reactor. The large amount production is based on long 60 day irradiation time. These are radionuclides for internal radiotherapy. [25]

^{188}W and ^{90}Sr are used in internal radiotherapy. The parent nuclide ^{188}W is produced by double neutron capture on ^{186}W in a high flux reactor for example at Oak Ridge, USA. ^{188}W/^{188}Re and ^{90}Sr/^{90}Y generator systems are used for production of ^{90}Y and ^{188}Re. ^{90}Sr is separated from fission products. Both ^{188}W and ^{90}Sr are produced in high specific activity close to the theoretical maximum. [15]

Molybdenum which is used in the ^{99}Mo/^{99m}Tc generator is produced in a reactor by either reaction of ^{98}Mo(n, γ)^{99}Mo or ^{235}U(n, f)^{99}Mo. Because of the relatively small cross section of the (n, γ)-reaction and natural molybdenum as target, the activity of produced ^{99}Mo is low. The natural molybdenum contains about 24 % of ^{98}Mo, which reduces the yield activity, which in turn leads to heavy loading of the Al2O3- generator column. Loading of the column adds the risk of breakthrough of molybdenum and makes the eluted ^{99m}Tc volumes large. High-flux nuclear reactors

have achieved higher specific activity of ^{99}Mo, but those are rarely available for nuclear medicine production. Mostly fission molybdenum is used though because of quality.[15]

The consumption of molybdenum-99 is calculated to be approximately 400 TBq per week. The main producers of ^{99}Mo are Nordion – NRU in Canada; Covidien – HFR in the Netherlands, BR2 in Belgium and Osiris in France; IRE Belgium – HFR, BRA and Osiris reactors; NTR – Safari reactor in South Africa. Molybdenum production is trying to meet the increasing demand by developing methods like the following for production [25]:

1. Highly enriched uranium is used as a target for ^{99}Mo production regularly, but low enriched uranium (LEU) is considered as an alternative for it. This would provide a larger availability of facilities to irradiate and process low enriched uranium. The use of LEU would also decrease the risk of nuclear weapon proliferation.

2. Water solution of uranyl sulfate or uranyl nitrate as reactor fuel in low power reactor of energy 20-200 kW. High level production is not yet possible but needs solving of chemical and technical problems. This type of high enriched uranium based developments are made in e.g. US (Covidien) and Russia.

3. Neutron capture of ^{99}Mo via reaction ^{98}Mo(n,γ)^{99}Mo and

4. accelerator production of ^{99}Mo.

$^{152}\mathrm{Sm}(n,\gamma)^{153}\mathrm{Sm}$ at reactor has a quite high cross section of 206 barn. Usually the nuclides made by the (n,γ)- reaction have a low specific activity, but the high cross section makes specific activity^{153}Sm higher. ^{32}P, ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I, ^{177}Lu and ^{188}Re are all produced with high specific activity via irradiations in nuclear reactors. [15]

Thorium-229 can be produced using reactor from neutron transmutation of ^{226}Ra,

^{228}Ra, ^{227}Ac and ^{228}Th. Neutron irradiation of ^{226}Ra produces thorium-229 by two β^- decays and three neutron captures. The dominant pathway is through ^{226}Ra $(n,\gamma) \rightarrow ^{227}$Ra $(\beta^-) \rightarrow ^{227}$Ac $(n,\gamma) \rightarrow ^{228}$Ac $(\beta^-) \rightarrow ^{228}$Th $(n,\gamma) \rightarrow ^{229}$Th. [26]

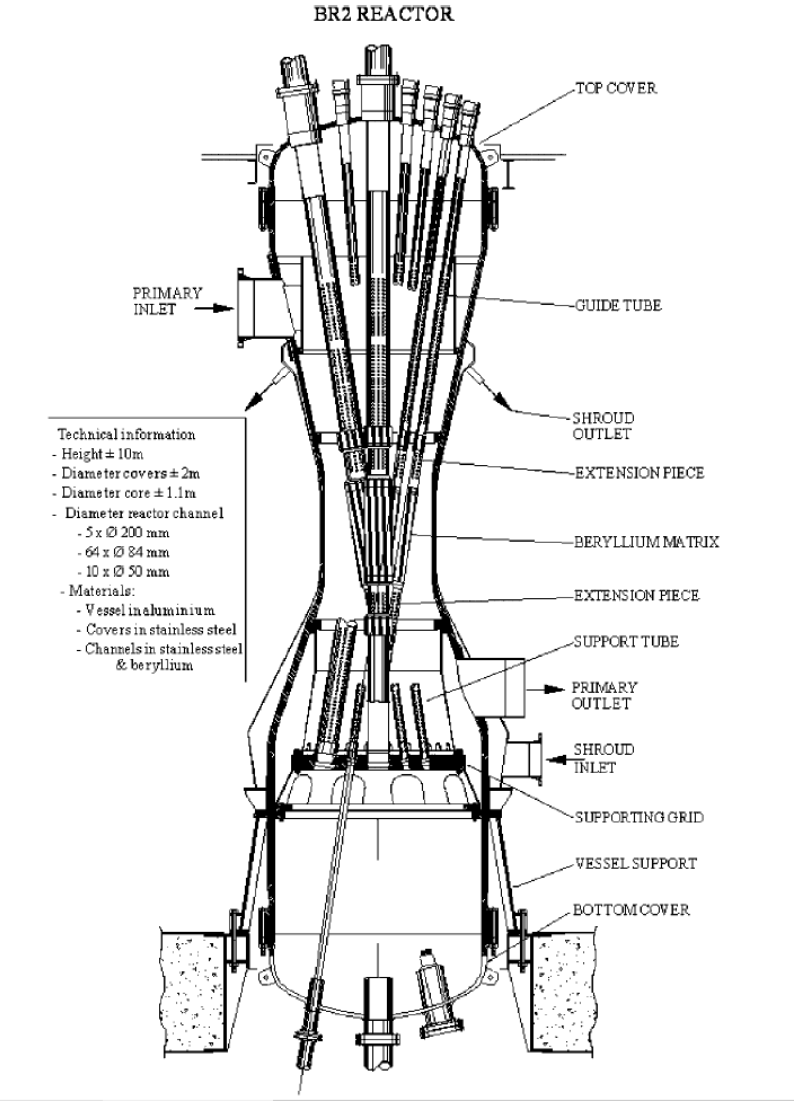

Figure 12. Cross section of a BR2 reactor [27].

Tin-117m decays via isomeric transition with emission of low energy conversion electrons and a gamma photon, which with the 159 keV gamma emission is suitable for imaging and dosimetric purposes. The conversion electrons deposit their energy (127, 129 and 152 keV) in a short range of 0,22-0.29 millimeters. ^{117m}Sn can be

produced via two routes – with radiative neutron capture on enriched ^{116}Sn or neutron inelastic scattering on enriched ^{117}Sn. The $^{116}\mathrm{Sn}(n_{ther},\gamma)^{117m}\mathrm{Sn}$ reaction has a theoretical cross section of 6 ± 2 millibarns and the $^{117}\mathrm{Sn}(n_{fast},n'\gamma)^{117m}\mathrm{Sn}$, which involves fast neutrons with an energy threshold of 318 keV has a cross section of 222 ± 16mb. The latter is reported to be the most attractive route to producing ^{117m}Sn in high flux reactors. Tin-117m has been produced for example in a BR2 reactor which is presented in figure 12.[27]

The BR2, whose cross-section is shown in figure 12, is a 100 MW high flux material testing reactor with a thermal neutron flux up to $10^{15}\frac{n}{\mathrm{cm^2s}}$. This high flux allows routine production of many medical and industrial isotopes. The BR2 reactor uses 93 % ^{235}U as fuel and is moderated by light water and beryllium. Its cooling water is at a temperature of $40-45$°celsius, and at pressure of 12 bars. It has seven irradiation channels with the best possible flux and peripheral reflector channels with peak thermal neutron fluxes from 1 to $3,5 \times 10^{14}\frac{n}{\mathrm{cm^2s}}$. [27]

The core of the BR2 reactor consists of beryllium hexagons with central irradiation channels, 32 fuel elements, seven control rods and a regulating rod [28]. Reactor operating between 50 to 70 thermal MW for 3 to 4 weeks is a standard irradiation cycle and operating at 58 thermal-MW over 21 to 28 days high specific activities of ^{117m}Sn can be achieved. Radionuclidic contaminants from the target were tested by Ge spectral analysis and Inductively Coupled Plasma Mass Spectrometry and they showed no metallic impurities. [27]

The targets are loaded into irradiation baskets inside the fuel elements. The neutron flux, depending on its position in the core and the burn-up, is $1-5\times10^{14}\frac{n}{cm^2s}$ above 0,1 MeV energy. The irradiation capsule is presented in figure 13. An example of the isotope production rate is presented in Figure 14, where the specific activity increases as a function of time. From the graph in Figure 14 can be seen how the half-live of ^{177}Lu ($T_{1/2} = 6.6$d makes the specific activity curve start to saturate as a half-live has passed. [28]

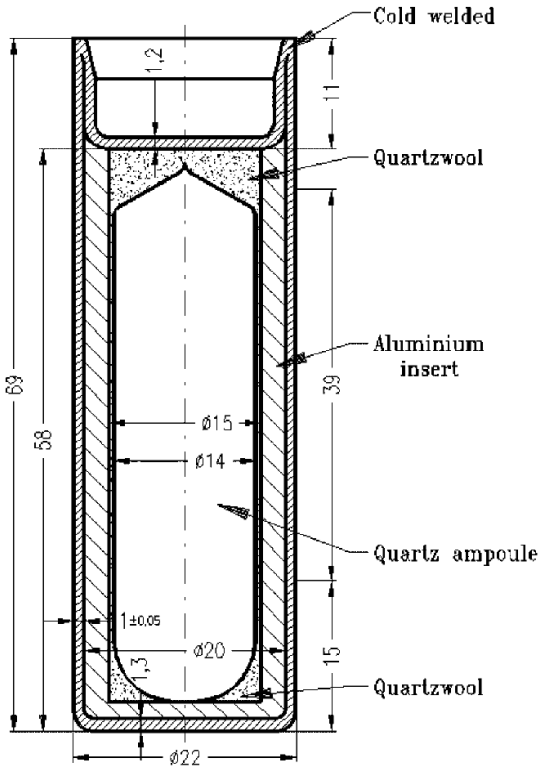

Figure 13. Irradiation capsule that is inside the fuel element. [28]

Fission is another way of producing isotopes for nuclear medicine by nuclear reactors. It is the dominant route of production for 99-Mo and 90-Sr , 131-I and 133-Xe. The chemical separation of a fission product usually lead to a product that is essentially free from stable isotopes and has a specific activity close to the theoretical maximum. [16]

Cumulative yield of ^{99}Mo in a thermal neutron induced fission is 6,16% with a cross section of 596 barn. A batch of ^{99}Mo could therefore be in TBq amounts. Basically only the fission produced molybdenum is accepted in the quality assurance, because it leads to high specific activity . Fission made ^{99}Mo is produced in a few centers and delivered around the world to laboratories and from there to clinics where estimated 35 million patients are diagnosed using^{99m}Tc. Other production method are discussed, since the nuclear rectors are ageing an there aren't plans for their replacement. Since the production route ^{235}U(n, f)^{99}Mo requires enriched uranium

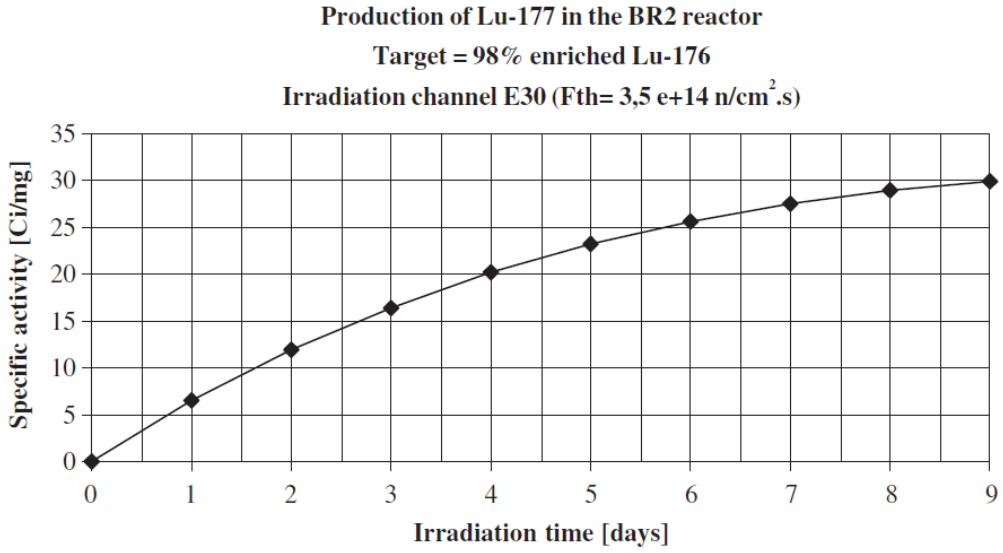

Figure 14. production of Lu-177 activity in the BR2 reactor with enriched Lu-176 as target as a function of irradiation time. [28]

as target, the reactors also bring up the risk of nuclear weapons. [15]

Accelerators and reactors are different as production methods and one of the advantages of accelerators is that they produce less than 10 % of the waste that the research reactors do. Accelerator waste is also less hazardous and they do not have the risk of proliferation of nuclear weapons. Reactors have also aged and there has been disruptions and scheduled shutdowns, which would indicate that the reactor production method might not be reliable no longer. Many radionuclides and their production routes, energy ranges and typical batch yields are listed in Table 6. [23]

Table 6. Some radionuclides and their properties based on paper by S. M. Qaim [15]

Nuclide	$T_{1/2}$	Decay	Production route	Energy (MeV)	Yield (GBq)
^{3}H	12.3 a	β^-	^{6}Li(n,α)	[i]	>500
^{11}C	20.4min	β^+	^{14}N(p, α)	3 - 13	100

Continued on next page

Table 6 – *Continued from previous page*

Nuclide	$T_{1/2}$	Decay	Production route	Energy (MeV)	Yield (GBq)
^{13}N	10.0min	β^+	^{16}O(p, α)	7 - 16	30
^{14}C	5730 a	β^-	^{14}N(n, p)	[i]	20
^{15}O	2.0 min	β^+	^{14}N(d, n)	0 - 8	100
			^{15}N(p, n)	0 - 10	
^{18}F	110min	β^+	^{18}O(p, n)	3 - 16	100
			^{20}Ne(d,α)	0 - 14	
^{32}P	14.3 d	β^+	^{32}S(n, p)	[ii]	> 100
^{67}Ga	3.26 d	γ (93),	^{68}Zn(p, 2n)^{67}Ga	18 - 26	50
		γ (185)			
^{68}Ga	68.3 min	β^+	^{69}Ga(p, 2n)^{68}Ge	13 - 22	5
			^{68}Ge$\rightarrow^{68}$Ga (gen.)		
^{82}Rb	1.3 min	β^+	^{nat}Rb(p, x)^{82}Sr	50 - 70	40
			^{82}Sr$\rightarrow^{82}$Rb(gen.)		
^{89}Sr	50.5 d	β^-	^{89}Y(n, p)	[ii]	20
^{90}Y	2.7 d	β^-	^{235}U(n, f)^{90}Sr	[i]	20
			^{90}Sr to ^{90}Y(gen.)		
^{99}Mo	2.75 d	β^-	^{235}U(n, f)^{99}Mo	[i]	> 10^3
^{99m}Tc	6.0 h	γ	^{98}Mo(n, γ)^{99}Mo	[i]	10
^{103}Pd	17.0 d	Auger e^-,	103Rh(p, n)	7 - 13	
		X-rays			
^{111}In	2.8 d	γ (173 keV),	^{112}Cd(p, 2n)^{111}In	18 - 25	50
		γ (247 keV)			
^{123}I	13.2 h	γ	^{123}Te(p, n)	10 - 14.5	20
			^{124}Xe(p, x)^{123}Xe$\rightarrow^{123}$I	23 - 29	70 [iii]
			^{127}I(p, 5n)^{123}Xe $\rightarrow$ ^{123}I	45 - 65	70 [iii]
^{125}I	59.4 d	Auger e^-,	^{124}Xe(n, γ)^{125}Xe$\rightarrow^{125}$I	[i]	50

Continued on next page

Table 6 – *Continued from previous page*

Nuclide	$T_{1/2}$	Decay	Production route	Energy (MeV)	Yield (GBq)
		X-rays			
^{131}I	8.0 d	β^-	^{130}Te(n, γ)^{131m,g}Te-^{131}I	[i]	> 100
			^{235}U(n, f)^{131}I	[i]	
^{153}Sm	1.9 d	β^-	^{152}Sm(n, γ)	[i]	>100 [v]
^{169}Er	9.4 d	β^-	^{168}Er(n, γ)	[i]	50 [vi]
^{177}Lu	6.7 d	β^-	^{176}Lu(n, γ)	[i]	50 [v]
			^{176}Yb(n, γ)^{177}Yb$\rightarrow$^{177}Lu	[i]	50
^{188}Re	17.0 h	β^-	^{186}W(n, γ)^{187}W(n, γ)^{188}W	[ii]	20
			^{188}W$\rightarrow$^{188}Re (gen.)		
^{201}Tl	3.06 d	X-rays, γ	^{203}Tl(p, 3n)^{201}Pb$\rightarrow$ ^{201}Tl	20 - 28	50 [iv]
^{211}At	7.2 h	α	209Bi(α, 2n)	20 - 28	< 5

[i] With reactor neutrons.
[ii] With neutrons in a high flux reactor.
[iii] ^{123}I yield after a 7 h decay of ^{123}Xe.
[iv] ^{201}Tl yield after a 32 h decay of ^{201}Pb.
[v] Product of moderate specific activity.
[vi] Product of low specific activity.

5 A brief overview of the possibilities of radioisotope production at JYFL-accelerator laboratory – study cases 18-F, 123-I and 225-Ac

In this chapter, I am giving illustrative examples and a brief overview on 18-F, 123-I and 225-Ac radioisotopes and their production at the accelerator laboratory of Jyväskylä University Physics Department (JYFL). These examples are the result of a literature review assignment as part of Research Training (FYSS9470 Erikoistyö) course during autumn 2018.

5.1 Actinium-225

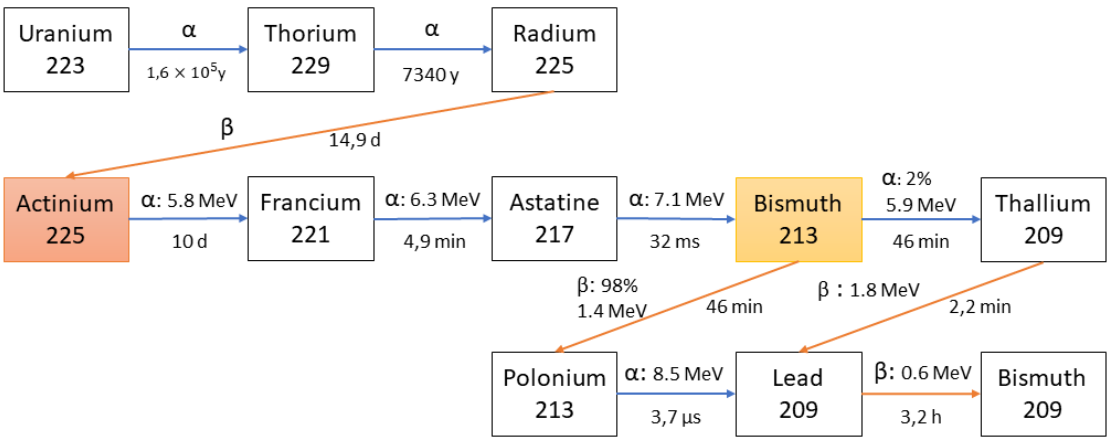

Figure 15. Actinium 225 production through Uranium-233 decay chain.

Actinium-225 has a half-life of 10 days. It's decay chain (Figure 15) has four alpha particle emitters with rather short half-lives from 46 minutes to 32 milliseconds.

Table 7. Possible reactions for actinium-225 production [34]

Possible production routes for ^{225}Ac
$^{232}\mathrm{Th}(n;\gamma,2\beta)^{233}\mathrm{U}$, $^{226}\mathrm{Ra}(3n,2\beta)^{229}\mathrm{Th}$, $^{226}\mathrm{Ra}(p,2n)^{225}\mathrm{Ac}$, $^{226}\mathrm{Ra}(n;2n,\beta)^{225}\mathrm{Ac}$, $^{226}\mathrm{Ra}(\gamma,n)^{225}\mathrm{Ra}$,

The decay chain would allow an effective treatment because once the actinium has reached its destination cell, one ^{225}Ac nucleus will give rise to four alphas, which then irradiate the cell eventually causing apoptosis due to increased DNA double-strand breaks. [29, 12]

Oak Ridge National Laboratory has been the main supplier of Actinium-225 since 1997 [26]. The actinium production at Oak ridge relies in the decay chain of ^{223}U presented in Figure 15. Thorium-229 stock at ORNL produces about 26 GBq of ^{225}Ac annually[26], but it is not enough to meet demand if it is found effective in studies. Second site that has a ^{229}Th source large enough is the Institute for Transuranium Elements in Karlsruhe, Germany, which has in a decade sent the amount of 3.5 Ci ($= 129,5$ GBq)[30] to hospitals and research centers. The separation of actinium from the thorium source can be performed in 2 to 3 days using nitric acid [30], which leaves days until the first half-life has passed. [30, 26, 31]

Both stocks of ^{229}Th originate from 1960's molten salt breeder reactors where ^{232}Th was irradiated by neutrons [29]. Unfortunately thorium has a long half-life of 7340 years thus only a fraction of it will decay to actinium-225 yearly making its availability very limited [32]. The production of ^{229}Th with neutrons would require ^{226}Ra to absorb three neutrons of unknown cross sections. This process would eventually lead to gain of ^{225}Ac, but it would require additional chemical processing which will probably lead to increased production costs. [33]

Possible artificial production ways for actinium could be based on irradiation of radium-226 with different particles or gamma rays [30]. Some of the possible reac-

tions for actinium-225 production are listed in Table 7. Accelerator based actinium production with protons is possible via nuclear reactions and short-lived parent nuclide decay or indirectly via the decay of radium-225 ($T_{1/2} = 14.9d$) [29].

The direct reaction to produce actinium-225 via nuclear reactions by proton bombardment is $^{226}\mathrm{Ra}(p, 2n)^{225}\mathrm{Ac}$, which requires cyclotron energies [33]. ITU in Karlsruhe found in their experiment that the maximum yields were at incident proton energies of 16.8 MeV [32]. Radium-226 in their experiment was obtained as radium carbonate, which was purified and dissolved with hydrogen chloride. The larger targets were made with 30 mg of radium-226 mixed with solution of $BaCl_2$ and HCl, which was evaporated and pressed into a $16\,\mathrm{mm} \times (0.8 - 1.0)\,\mathrm{mm}$ pellet [32]. The pellets were welded into leak-tight silver capsules, which were monitored for leaks by observing alpha activity in the cooling water system during irradiation. [32]

The pellet targets were irradiated using $\approx$ 16MeV protons with varying irradiation times and were let cool for 2-3 days. After the cooling period they were opened in a hot cell and the contents was dissolved in a 0.01 M HCl and was analyzed. Extraction chromatography was used to separate actinium-225 and radium from the solution and the radium eluate was analyzed and conditioned for another target preparation. [32]

Cross sections for the reaction were determined experimentally and they are in correlation with ALICE code model calculations. Maximum cross sections and therefor yield were detected at proton energies of 16.8 MeV, which can be seen also in Figure 16. In this energy region competing reactions producing ^{224}Ac and ^{226}Ac were found negligible compared to the purity of ^{225}Ac. ^{224}Ac ($T_{1/2} = 2.9\,h$) has time to fully decay to ^{224}Ra during the cooling time, thus it doesn't contaminate of the product. ^{224}Ra and ^{225}Ra formed in the reaction are removed in the Ra/Ac-separation.[32]

The radium target is radioactive even before bombarding thus radiation safety must be accounted for. As can be seen from Table 8 The radiation dose one meter from

Table 8. Radiation dose rates caused by radium-225 sources [33]

Activity in Bq	Activity in Ci	Dose rate (Sv/h) 1 m from source
1 MBq	0.027 mCi	0.23 μSv/h
740 MBq (stand. ^{226}Ra needle)	20 mCi	0.17 mSv/h

a standard radium needle used in medicine in a time period of one hour would be 1.7 mSv [33]. This equals around half of the average annual radiation dose of one resident of Finland [8]. The maximum annual radiation dose for the public in Finland due to nuclear energy or other classified radiation practices is 1 mSv. The limit is defined in the STUK – Radiation and Nuclear Safety Authority (Finland) guide ST 7.2 (2014) and does not include natural background radiation. Possible solutions for radiation protection besides shielding could be remote controlled target placing and handling small batches of radium at a time [33].

Actinium could as well be used as a generator nuclide, because it decays to Bismuth-213, which is likewise an alpha emitter and can be used in radioimmunotherapy. ^{213}Bi has short half-life of 46 minutes and high energy 8.4 MeV alpha emission. [33]

Alpha particles have a high LET value and a short range in tissue, which makes alpha emitters advantageous compared to beta emitters. High LET radiation is more cytotoxic than low LET, because high LET alpha radiation gives rise to more biological damage over short distance than low LET beta does. Alpha emitters are therefore especially useful for targeted therapies, where the nuclide is taken to the treatment site by vectors which allows non-localized diseases like leukemia or metastases to be treated. [34, 29]

The idea behind Targeted Alpha Therapy is that a molecule targeting membrane bound molecules on cancer cell surface is attached to a cytotoxic radioactive substance. Radioisotopes themselves usually cannot target cancer cells, which is why specific targeting vectors are needed. Cancer cells over-express antigens on their

membranes and those can be targeted by these vectors, such as mAbs. Together the vector and the radioisotope form an alpha-immunoconjugate [14].

Currently isotopes considered for Targeted Alpha Therapy are Bi-213, At-211 and Ra-225 [30]. Bismuth-213 is a daughter nuclide of ^{225}Ac and it can be produced via generator system in similar manner as the molybdenum/technetium generator (discussed in Chapter 4.2) [33].

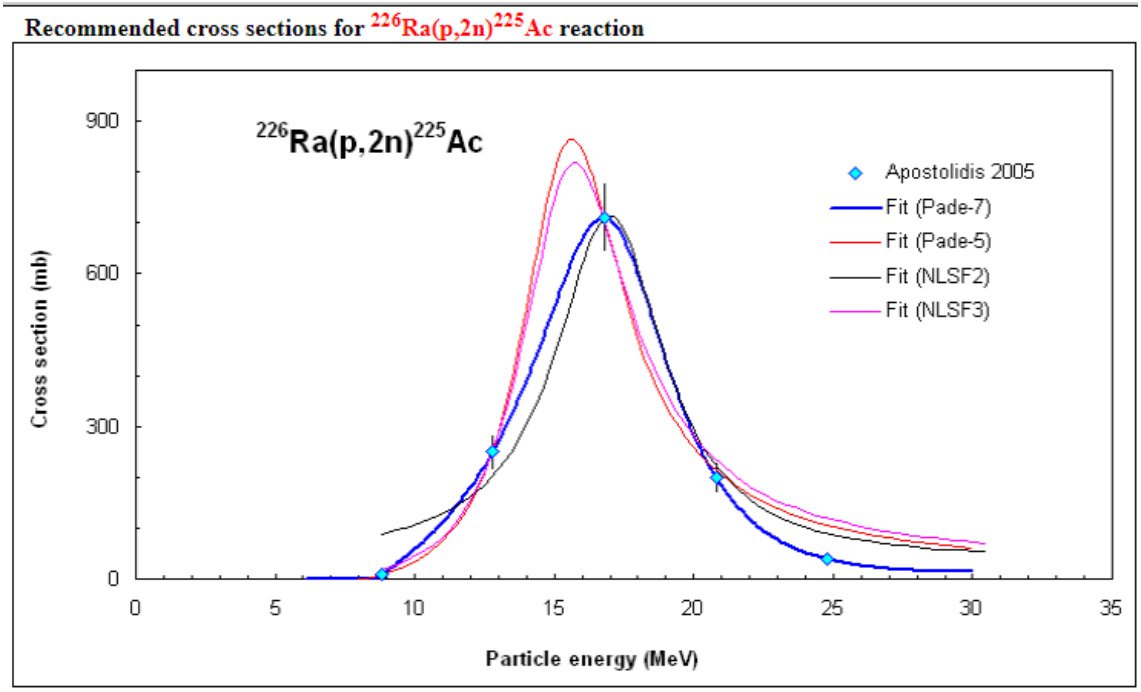

Figure 16. The cross sections of Actinium production via reaction ^{226}Ra(p,2n)^{225}Ac measured by Apostolidis et al. [32] and decay data by H. Xiaolong and W. Baosong (Evaluation of ^{225}Ac decay data, Applied Radiation and Isotopes 65 (2007) 712).

Table 9. Reactions for production of Iodine-123 for medical use [35]

Possible production routes for ^{123}I
^{121}Sb$(\alpha, 2n)$, ^{122}Te(d, n), ^{123}Sb$(\alpha, 4n)$,
^{123}Te$(d, 2n)$, ^{123}Te(p, n), ^{124}Te$(d, 3n)$,
^{124}Te$(p, 2n)$, ^{125}Te$(p, 3n)$, ^{126}Te$(p, 4n)$,

5.2 Iodine-123

Iodine-131 is the oldest theranostic agent, was first produced in 1949, nowadays frequently used as a scanning agent in radiotherapy [36]. Iodine-123 ($T_{1/2} = 13.27h$) is utilized in SPECT and is produced using cyclotrons and highly enriched targets. Presently I-123 is produced using gas targets of highly enriched Xe-124. The target is bombarded with protons and it relies in the decay chain of Cesium-123 which decays through Xenon-123 to Iodine-123. A long lived isotope, Tellurium-121, might be co-produced, because of the reaction ^{124}Xe$(p, \alpha)^{121}$I. The gas targets are let cool for hours to ensure the growth of ^{123}I by the decay of its parent nuclides. The optimal in-growth time for ^{123}I is 6.6 hours in which the maximum yield is obtained. Some of the other possible reactions for ^{123}I production are listed in table 9.[37]

Commercial facilities though perform irradiations up to 20 hours, which result in large quantities of ^{123}I. Because the Iodine in-growth happens during the irradiation, the cooling times can be determined as a function of decay of the contaminants rather than for maximum in-growth of I-123. [37]

An experiment was made in which custom-made ^{124}Xe gas cell targets were bombarded with protons of 17 different incident energies between 9 to 38 MeV to determine the cross section of ^{121}I, ^{123}Cs and ^{123}Xe(cumulative). [37] In this experiment after irradiation the gas targets were let cool for a few minutes to let the most short lived contaminants decay. The closed gas cells are placed for five minutes into water

of 0 degrees celsius, to let the Cesium and Iodine isotopes settle onto the wall of the cell. The activity and decay or in-growth times for Cs, Xe and I isotopes of interest were followed using gamma-ray spectroscopy for repeated 5 minute periods until 1-2 hours after end of bombardment. [37]

The remaining Xenon gas isotopes were cryogenically recovered at the end of the measurement. The target cells were then filled with solution of $NaI/NaHSO_3/HNO_3$ and shaken to recover most of the radioiodine on the cell walls. The solution formed in this rinsing is collected and the cell is again rinsed with the $NaI/NaHSO_3/HNO_3$ solution to further collect all the formed iodine. The solution with the radioiodine was then filtered and the filter dried. The efficiency of this procedure to recover Iodine-123 was determined to be around 60%, due to possible losses during different steps of the procedure, by measuring its activity.

The precipitate, formed in the procedure explained above, contains only the Iodine that formed during the irradiation period, because all of the Xe was collected after the end of bombardment. Therefor the total possible activity could not be determined. [37]

The contamination of ^{121}Te is inevitable with a reaction cross section maximum at 20 MeV. Its parent nuclide ^{121}I is short-lived with a half-life of 2.12 hours with 94 % EC and 6% positron emission. The accumulation of Tellurium, the half-life of which is 16.8 days, will impair the product of use after multiple ^{123}I half-lives.[37]

Hermanne et al. followed the formation of Tellurium-121 by recovering quantitatively the Iodine isotopes that were formed in the irradiation and decay less than two half-lives of Xenon-123 ($T_{1/2}$ = 2.08h) after end of bombardment. This means that not all of the Xenon-123 had yet in that time decayed to Iodine-123, so the total cumulative of Iodine-123 could not be determined. The decay curve of ^{121}Te was followed, but the measurements weren't in good correlation with the activity of ^{121}I present in the cells. [37]

Production of ^{123}I with electron accelerator via reaction $^{124}\mathrm{Xe}(\gamma, n)^{123}\mathrm{Xe}$ would be more efficient compared to linear accelerators and cyclotrons economically. The electron beam is converted via bremsstrahlung into a photon beam which is then used to induce the reaction above. Nuclear codes TALYS 1.6 and EMPIRE 3.2. have been used to calculate the cross section for the production of ^{123}Xe and its maximum is at gamma energy of 15 MeV with cross section values of $230 - 264\,\mathrm{mb}$. Threshold for this reaction is -10.4MeV [38, 37]

The peak value for direct production of ^{123}I via reaction $^{124}\mathrm{I}(\gamma, p)^{123}\mathrm{I}$ is around 3.5 mb, which is rather small compared to other reactions [38]. In the experiment performed by Avetisyan et al. the target had around 40 grams of natural Xenon in pressure of about 200 bars, which further increased up to 250 bars during the irradiation. The irradiation time was 12 hours after which the target was first let cool for 4 hours and then the ^{123}I was cryogenically extracted. The normalized specific activity of ^{123}I obtained in the experiment was $143\frac{\mathrm{Bq}}{\mathrm{mg}\cdot\mu\mathrm{A}\cdot\mathrm{h}}$ and it is in good agreement with other published results. [38]

In practice the only reaction in which ^{121}I can be formed in the experiment conditions (proton energy between 13 to 37 MeV) is the direct production via $^{124}\mathrm{Xe}(p, \alpha)^{121}\mathrm{I}$ reaction. It has a theoretical threshold of $+3.8$MeV and the same value for reaction with the separate nucleons exiting has a theoretical threshold of -24.8MeV and was expected to contribute above 30 MeV, but the expected rise was not observed in Hermanne et al. study. [37] The cross sections measured by Hermanne et al. for Xenon-123 production are plotted in Figure 17.

^{123}I doesn't have a beta emission, so its dose in imaging to the thyroid is less than one percent of the dose given by ^{131}I. [38] It has a lower energy (159 keV gamma) compared to ^{131}I making collimation of ^{123}I more efficient. It decays 100 % by electron capture. In a positive sense ^{123}I half-life of 13.27 hours allows it to be shipped to the site of use, but its biological half-life is shorter than of ^{131}I ($T_{1/2} = 8.0d$), which further decreases the dose of ^{123}I. Some of the properties of different iodine

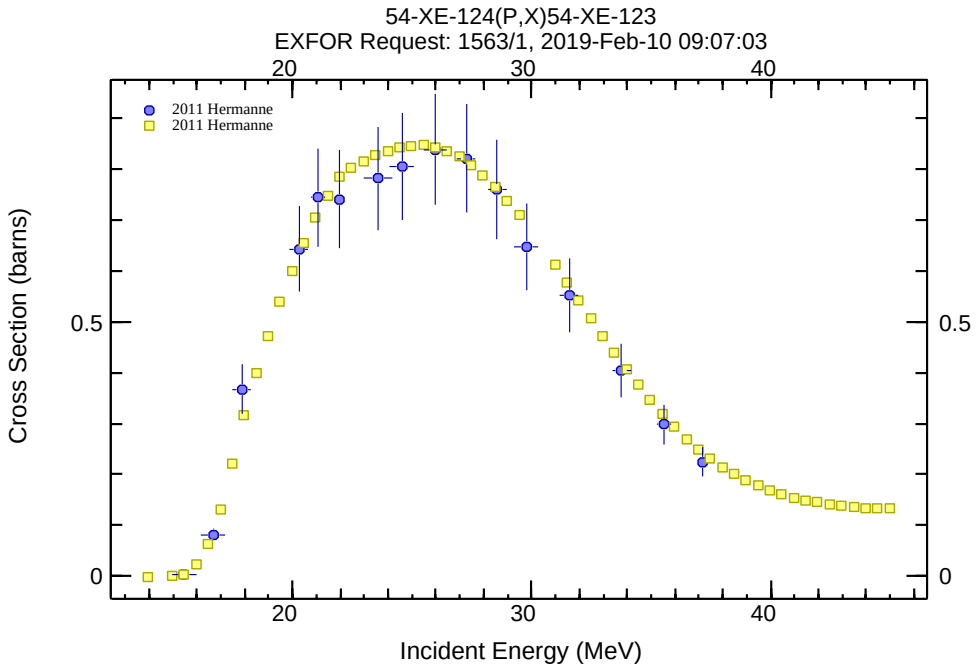

Figure 17. The reaction cross section of ^{124}Xe(p, x)^{123}Xe reactions as function of incident proton energy measured by Hermanne et al [37]. Figure is from https://www-nds.iaea.org/exfor/endf.htm IAEA database

isotopes are given in table 10, which shows that ^{123}I has 25.03 photon emissions per minute whereas ^{131}I has only one per minute. [37]

Clearly the difficulty of producing Iodine-123 in the case described above is the fact that the target, Xenon, is in a gaseous form. In order to make the irradiation efficient the target gas must be in high pressure to make the probability of the beam hitting the gas nuclei high. On the bright side, Xenon is a noble gas so it is not reactive in any case which makes it rather safe to use. Use of an enriched Xe-124 target is more expensive than the natural Xenon targets, but they can be used multiple times by recovering ^{124}Xe and they will also rule out the contamination of Iodine-125. Enriched ^{124}Xe target increases the ^{123}I activity by more than 100 times [38].

The contamination of the product with ^{121}Te is also an issue, because of its long half-live. [37, 38]

Table 10. Comparison of Iodine isotopes [35]

Isotope	Photopeak (MeV)	Detectable photons/min/rad relative to ^{131}I 24 hours after administration
I-123	0.159	25.03
I-124	0.511	0.54
I-125	0.035	3.11
I-126	0.386	0.44
I-128	0.441	Half-life too short for 24-h study
I-130	0.538	2.00
I-131	0.364	1.00
I-132	0.668	0.03

5.3 Fluorine-18

^{18}F is commonly used in positron emission tomography. It decays 100% by positron emission, with positron energy of maximum 635 keV with 2.3 mm range in soft tissue [39]. Fluorine-18 like most PET isotopes require less than 20 MeV proton beam to be produced by nuclear reactions for which medical PET cyclotrons are developed for. They have a 50-100 μA current capacity and they an produce large amounts of PET isotopes with proton and deuteron beams. Typical current for PET isotope production is around 250 μA. [39, 40]

There are two chemical forms of ^{18}F produced via reactions $^{20}\mathrm{Ne}(d,\alpha)^{18}\mathrm{F}$ and $^{18}\mathrm{O}(p,n)^{18}\mathrm{F}$. The isotope produced in the first reaction is in a highly reactive electrophilic form obtained using ^{19}F carrier, which decreases the specific activity of ^{18}F. The second reaction provides nucleophilic fluoride ion and can be performed on

either enriched ^{18}O water, which will give a high specific activity, or on oxygen-18 gas target which needs ^{19}F carrier to recover ^{18}F activity from the target. [39]

Presently Fluorine-18 is most commonly produced by irradiating enriched ^{18}O water with protons of energies from 2.57 MeV to 20 MeV. It is obtained with high specific activity (185 GBq μmol^{-1}) as an anion [^{18}F]fluoride in a water solution. The solution is usually transferred through semi-permanent tubing in PET facilities. ^{18}F has a half-life of 109.77 minutes, which is rather long compared to the half-lives other PET isotopes like carbon-11 ($T_{1/2} = 20\,\text{min}$) and nitrogen-13 ($T_{1/2} = 10\,\text{min}$), oxygen-15 ($T_{1/2} = 2\,\text{min}$). The half-life is long enough to allow radiopharmaceutical medication to be labelled and delivered to the site of use. The shelf-life of ^{18}F is the order of hours and the preferred synthesis time in clinical studies is less than two hours. [39, 22, 41, 42]

Other than proton bombarding, deuterons are also considered for fluorine-18 production via reactions $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$ and $^{17}\text{O}(d,n)^{18}\text{F}$. These reactions have no threshold, but the deuteron energy has to overcome the Coulomb barrier. The cross section of the deuteron on Neon-20 target at 2.5 MeV is about 80 millibarns, which is large enough for reasonable amounts of ^{18}F to be produced. Deuteron induced PET isotope production is of interest because of its possible lower cost. [40]

The modern ^{18}O water target, also called a batch boiling water target, is made of niobium or tantalum metals, which can withstand the aggressive irradiation and the erosion caused by the beam. The erosion leads to leak of impurities to the target water, which leads to deterioration of the product reactivity. and heat elevation. Havar foil is usually used as the target entrance foil. The target is an area of development still even though there has been many advances before reaching the mentioned materials. The design basis of the boiling water target has been very much empirical, but there has been an increase in modeling of the targets thermal processes, which has lead to enhanced target and production capabilities. [42, 22]

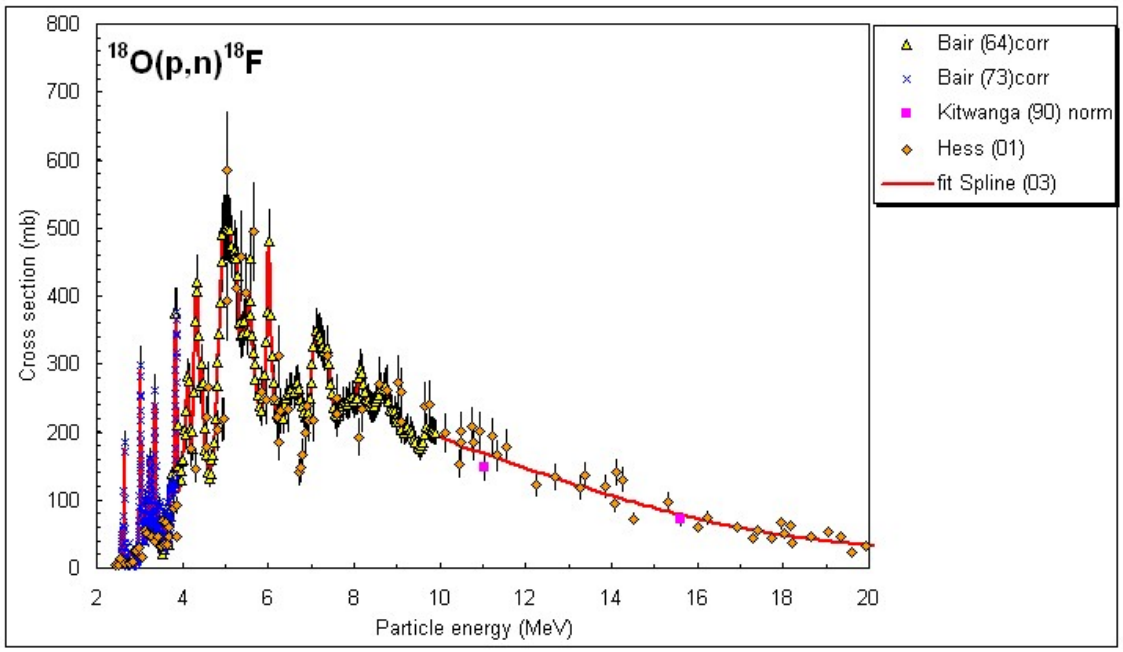

Figure 18. The experimental cross sections for fluorine-18 production from oxygen-18 target bombarded with protons presented as function of proton energy.

Figure 18 presents experimental ^{18}F cross sections in ^{18}O(p, n)^{18}F reactions as function of incident particle energy likewise Figure 19 presents the cross sections of ^{Nat}Ne(d, x)^{18}F reactions as function of incident particle energy. The maximum cross sections in ^{18}O(p, n)^{18}F reactions occur around 5 MeV proton energies with values under 600 millibarns. The corresponding values for natural neon are around 6 MeV and approximately 230 millibarns respectively. This would imply that the production of fluorine-18 would be more efficient using ^{18}O as a target. [42, 22]

5.4 Radioisotope production in the accelerator laboratory

Essential properties in isotope production in an accelerator laboratory are e.g. the energy at which the best yield is given and the time that the target should be bombarded.

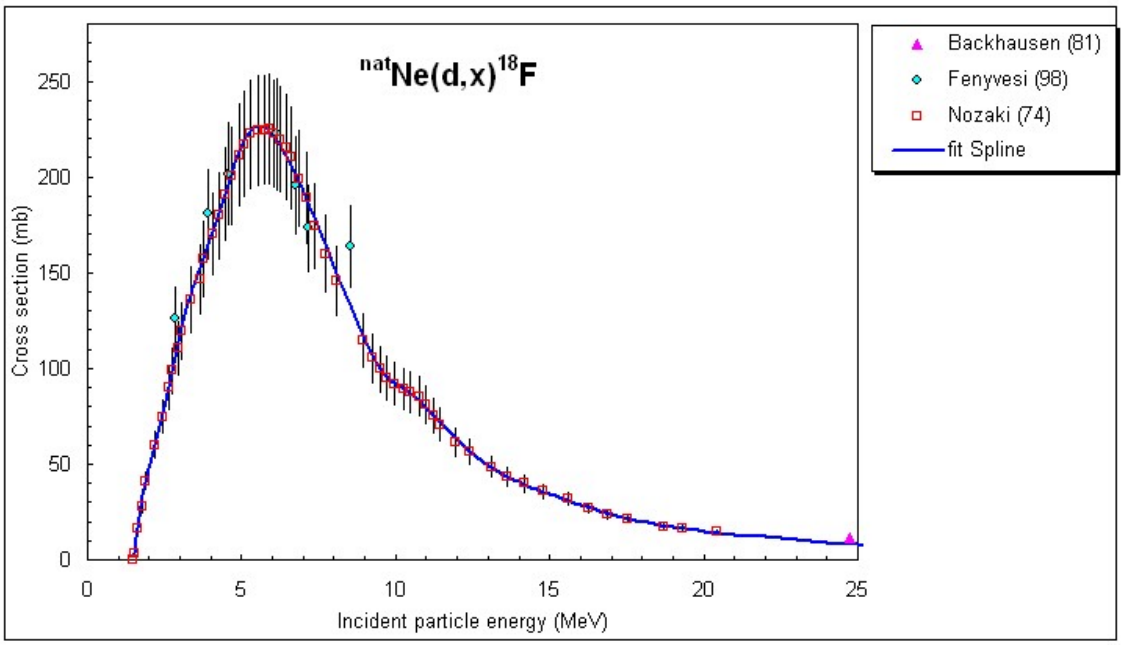

Figure 19. The experimental cross sections for fluorine-18 production from natural neon target bombarded with deuterons presented as function of deuteron energy.

The irradiation time seldom exceeds three half-lives,unless the isotope is short lived, because the saturation of activity increase is almost 90 % at $t \approx 3\,t_{1/2}$. The half-life of an isotope therefor defines the practical limits for irradiation times. The saturation, or build-up factor $B = (1 - e^{-\lambda t_{irr}})$, is plotted as a function of irradiation time in figure 10. [43] In reality the irradiation times are limited also by other reasons like the cost of beamtime and how long it is possible to maintain a stable beam current.

Lets consider the highest achieved cross section as the best possible approximation. The typical beam current of MCC-30 accelerator in the Accelerator laboratory of The University of Jyväskylä's physics department is $I = 100\,\mu A$. The build-up of actinium-225 with accelerator beam current $100\,\mu A$ in 5 days or 120 hours is approximately 880MBq. The build-up curve for actinium-225[i] is shown in figure 20

[i]The saturation activity for actinium-225 used in this calculation is $30\,\frac{\mathrm{MBq}}{\mu\mathrm{A}}$ [A. Virtanen and J. Kumpulainen, private communication].

and the calculation is shown here:

$$\begin{aligned} A_{EOB}(^{225}\mathrm{Ac}) &= A_{sat}(^{225}\mathrm{Ac}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}}}) \cdot I \\ &= 30\,\frac{\mathrm{MBq}}{\mu\mathrm{A}} \cdot (1 - e^{-\frac{ln(2)\cdot 5\mathrm{d}}{10\mathrm{d}}}) \cdot 100\,\mu A \\ &= 878.679 \approx 880\,\mathrm{MBq}. \end{aligned}$$

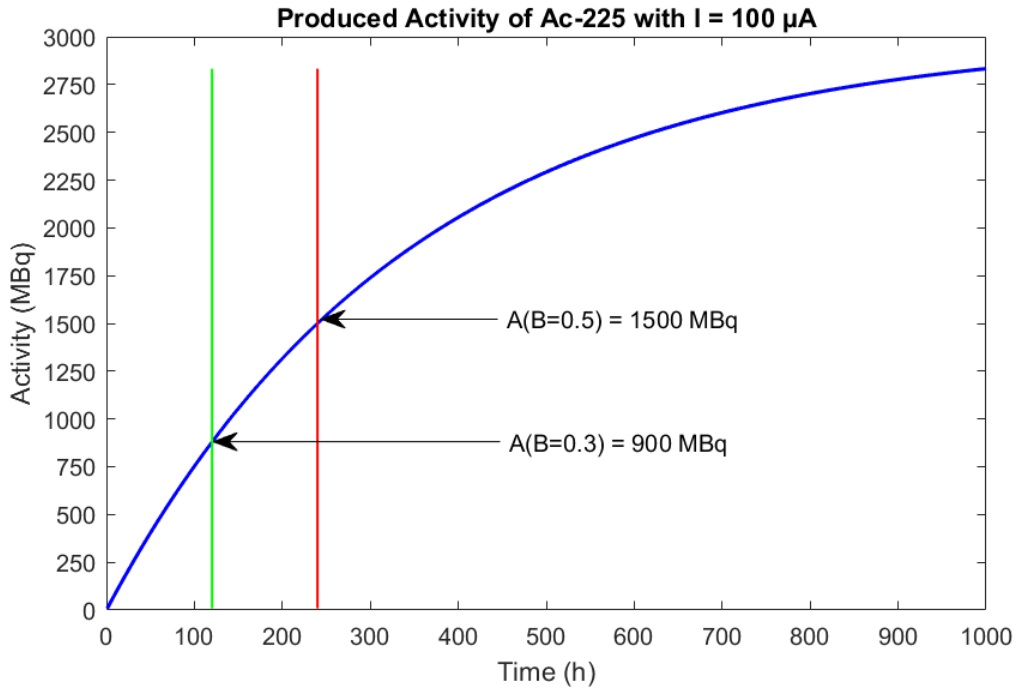

Figure 20. Activity curve of actinium-225 as a function of irradiation time shows how much activity is produced during $B = 0.5$, which corresponds approximately one half-life, and half a half-life ($B \approx 0.3$). Plot and results are made using MATLAB 2016b

The same calculation were made for fluorine-18 production using saturation activity value for fluorine-18. The maximum cross section of 502 mb found is at 5.0 MeV with a corresponding saturation activity of 1.17 GBq/μA [A. Virtanen and J. Kumpulainen, private communication].

$$\begin{aligned} A_{EOB}(^{18}\mathrm{F}) &= A_{sat}(^{18}\mathrm{F}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}}}) \cdot I \\ &= 1.17\,\frac{\mathrm{GBq}}{\mu\mathrm{A}} \cdot (1 - e^{-\frac{ln(2)\cdot 60\,\mathrm{min}}{109.77\,\mathrm{min}}}) \cdot 100\,\mu A \\ &= 36.897\ldots \approx 36.9\,\mathrm{GBq}. \end{aligned}$$

The production of activity with respect to irradiation time is plotted in figure 21. These calculations do not take error factors into account so they need to be considered as possible demeaning factors with production yields. Eventually the actual end of bombardment activity will depend also on the target thickness, which is included in the saturation activity.

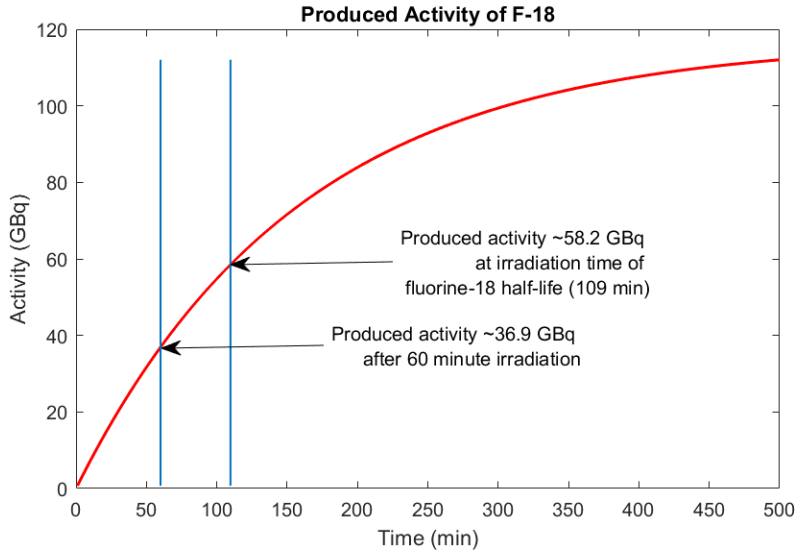

Figure 21. Plotted activity curve of fluorine as a function of irradiation time. Plot and results are made using MATLAB 2016b

The normalized specific activity of iodine-123 in Hermanne et al. study was found to be 143 $\frac{\text{Bq}}{\text{mg}\cdot\mu\text{A}\cdot\text{h}}$. Using this information with irradiation time of 6 hours, the activity produced would be

$$A_{EOB}(^{123}\text{I}) = 143\frac{\text{Bq}}{\text{mg}\cdot\mu\text{A}\cdot\text{h}}\cdot 100\,\mu A\cdot 6\,\text{h} = 85.8\frac{\text{kBq}}{\text{mg}},$$

via the ^{124}Xe(p, x)^{123}Xe reaction.

In Figure 22 the production of iodine-123 using cyclotron via ^{124}Xe(p, 2n)^{123}Cs is presented.

The yields in Figure 22 can be calculated through the following three equations:

$$A_{EOB}(^{123}\text{Cs}) = A_{sat}(^{123}\text{Cs})\cdot(1-e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\text{Cs})}})\cdot I$$

$$A_{EOB}(^{123}\mathrm{Xe}) = A_{sat}(^{123}\mathrm{Cs}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\mathrm{Cs})}}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\mathrm{Xe})}}) \cdot I$$

$$A_{EOB}(^{123}\mathrm{Xe}) = A_{sat}(^{123}\mathrm{Cs}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\mathrm{Cs})}}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\mathrm{Xe})}}) \cdot (1 - e^{-\frac{ln(2)\cdot t_{irr}}{T_{1/2}(^{123}\mathrm{I})}}) \cdot I$$

The saturation activity of cesium-123 ($T_{1/2} = 5.82\,\mathrm{min}$) limits the activity of xenon-123 ($T_{1/2} = 1.95\,\mathrm{h}$) and iodine-123 ($T_{1/2} = 13.2\,\mathrm{h}$), because they are the decay products of cesium. After the irradiation time of 6 hours the beam is stopped and the produced activity of iodine-123 rises, but soon starts to decrease. From Figure 22 the practical activity of the iodine product is approximately 75 GBq 12 hours after the start of bombardment when delivered to a factory for further refinement.The current of the beam in this case is 50 μA and the proton energy is 30 MeV. [A. Virtanen and J. Kumpulainen, private communication]

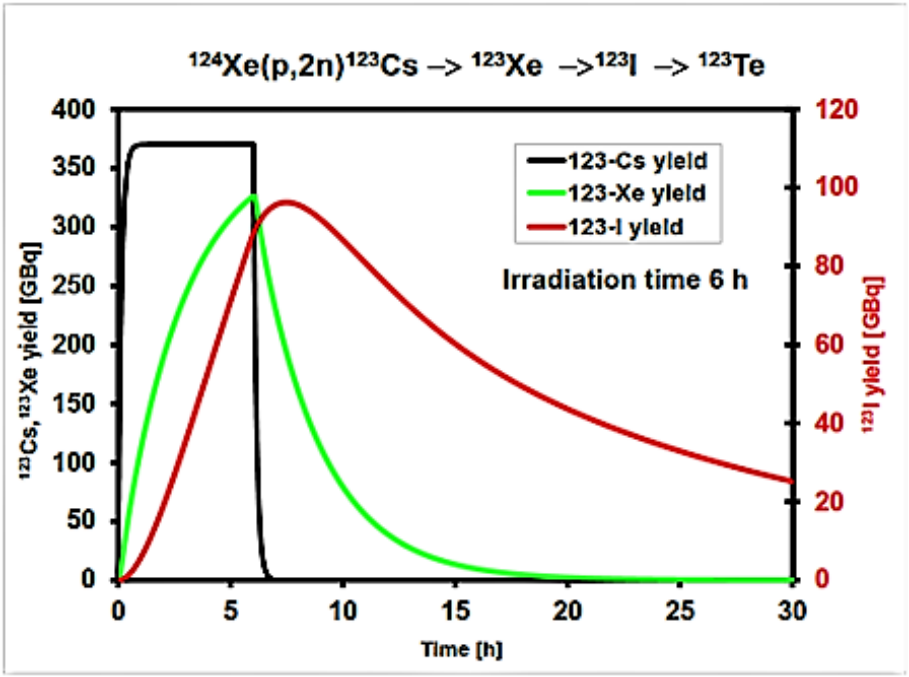

Figure 22. The activities of Ce-123, Xe-123 and I-123 produced in cyclotron are plotted as a function of irradiation time with proton energy of 30 MeV, beam current $I = 50\mu A$ [A. Virtanen and J. Kumpulainen, private communication].

6 Conclusions

The object of this thesis was to look into the methods of medicinal isotope production and their purpose of use to compare features and to study the capabilities of cyclotron production.

Nuclear medicine is a rather old method of treating and imaging diseases and it is also an important part of modern medicine. Radioactive nuclides are used in imaging and treating patients without giving unnecessary dose or health hazard. There are various ways of producing radioisotopes for use in medicine. Most nuclides are manufactured with reactors or cyclotrons and some of them can be produced on both, but others need one or the other method. Positron emitters can only be made by cyclotrons, but then again high specific activity of molybdenum is only achieved in nuclear reactors. These methods are therefor complementary to each other and neither is unambiguously better than the other.

University of Jyväskylä Physics department has the MCC-30 accelerator, which has not yet been used to produce radionuclides and the prospects of its utilization in this sense are being looked into. The theoretical yields for actinium-225, iodine-123 and fluorine-18 were calculated in Chapter 5.4. In order to calculate these with better accuracy, the specifications of the targets should be precise.

The practical yield of the products depends on the specifications of the target and the beam in cyclotron production. The irradiation time as a feature of the beam affects the yield because of practical limitations and it is also proportional to the half-life of the product. Generally high specific activity is produced if the product nuclide is chemically separable from the target nuclide and possible contaminant

isotopes can be removed. This increases the yield and improves the quality of the product. The half-life of the product defines the possible distance where it can be transported and limits the time for further processing.

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