TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

Инженерная школа ядерных технологий
Направление подготовки 14.04.02 Ядерные физика и технологии
Отделение ядерно-топливного цикла

МАГИСТЕРСКАЯ ДИССЕРТАЦИЯ

Тема работы
Получение радионуклида ^{177}Lu для ядерной медицины методом цементации на исследовательском реакторе ИРТ-Т

УДК 621.384.664: 621.039.55: 615.615.84

Студент

Группа	ФИО	Подпись	Дата
0АМ0М	Мере Пабалло Ангела		04.06.2022

Руководитель ВКР

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ШИП	Тимченко С.Н.	к.т.н		

КОНСУЛЬТАНТЫ ПО РАЗДЕЛАМ:

По разделу «Финансовый менеджмент, ресурсоэффективность и ресурсосбережение»

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ОСГН ШИП	Спицына Л.Ю.	к.э.н.		

По разделу «Социальная ответственность»

Должность	ФИО	Ученая степень, звание	Подпись	Дата
Доцент ОЯТЦ ИЯТШ	Передерин Ю.В.	к.т.н		

ДОПУСТИТЬ К ЗАЩИТЕ:

Руководитель ООП	ФИО	Ученая степень, звание	Подпись	Дата
Nuclear medicine / Ядерная медицина	Мере П.А,	к.и.н.		

Томск – 2022 г.

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School of Nuclear Science & Engineering
Field of training: 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine

MASTER THESIS

Topic of research work
Production of ^{177}Lu radionuclide by cementation method for nuclear medicine at the research reactor of the IRT-T

UDC 621.384.664: 621.039.55: 615.615.84

Student

Group	Full name	Signature	Date
0AM0M	**Mere Paballo Angelah**		**04.06.2022**

Scientific supervisor

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	**Timchenko S.N.**	PhD		

ADVISERS:

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	Luibov Y. Spicyna	PhD		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate Professor	Yuriy V. Perederin	PhD		

ADMITTED TO DEFENSE:

Programme Director	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Vera V. Verkhoturova	PhD		

Tomsk – 2022 г

LEARNING OUTCOMES

Competence code	Competence name
Universal competences	
UC(U)-1	Ability to make critical analysis of problem-based situations using the systems analysis approach, and generate decisions and action plans.
UC(U)-2	Ability to run a project at all life-cycle stages.
UC(U)-3	Ability to organize and lead the teamwork and generate a team strategy to achieve the target goal.
UC(U)-4	Ability to use modern communication technologies to realize academic and professional interaction.
UC(U)-5	Ability to analyze and account for cultural diversity in the process of intercultural interaction.
UC(U)-6	Ability to set and pursue individual and professional activity priorities and ways to modify professional activity based on the self-esteem.
General professional competences	
GPC(U)-1	Ability to formulate goals and objectives of the research study, select assessment criteria, identify priorities for solving problems.
GPC(U)-2	Ability to apply modern research methods, evaluate and present the results of the performed research.
GPC(U)-3	Ability to present research outcomes in the form of articles, reports, scientific reports and presentations using computer layout systems and office software packages.
Professional competences	

PC(U)-1	Ability to maintain medical and technical documentation related to medico-physical aspects of radiation therapy, interventional radiology and radionuclide diagnostics and therapy.
PC(U)-2	Ability to ensure radiation safety of personnel, public, and the environment, to carry out monitoring of radiation exposure levels of patients, personnel, public, and the environment.
PC(U)-3	Ability to operate and maintain equipment and tools applied for the medical use of radiation.
PC(U)-4	Ability to manage the quality of physical and technical aspects within radiation therapy, diagnostics, interventional radiology and radionuclide diagnostics and therapy departments in accordance with the specific equipment requirements, regulatory requirements and staffing of a medical organization.
PC(U)-5	Ability to conduct and organize dosimetry planning, clinical dosimetry, quality assurance procedures for radiotherapy, interventional radiology, and radionuclide diagnostics and therapy.
PC(U)-6	Ability to apply knowledge of natural sciences, fundamental laws in the field of nuclear physics and technology, clinical and radiation standards, hygienic measures in nuclear medicine, which is sufficient to study issues associated with medical physics using modern equipment and information technology relying on the latest Russian and international experience.
PC(U)-7	Ability to develop reference books, tables and software containing data for clinical use in dosimetric planning of radiation therapy, radionuclide diagnostics and therapy.

PC(U)-8	Ability to take part in the design and physical and technical equipment development for radiation therapy, diagnostics, interventional radiology and radionuclide diagnostics and therapy, and radiation safety divisions.
PC(U)-9	Ability to conduct training sessions and develop instructional materials for the training courses within the cycle of professional training programs (bachelor degree programs).

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School of Nuclear Science & Engineering
Field of training: 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine
Nuclear Fuel Cycle Division

APPROVED BY:
Program Director
_____ Verkhoturova V.V.
«____» _____ 2022

ASSIGNMENT

for the Graduation Thesis completion

In the form:

Master Thesis

For a student:

Group	Full name
0AM0M	Mere Paballo Angelah

Topic of research work:

Production of ^{177}Lu radionuclide by cementation methods for nuclear medicine at the research reactor of the IRT-T	
Approved by the order of the Director of School of Nuclear Science & Engineering (date, number):	№ 32-6/c dated February 1, 2022

Deadline for completion of Master Thesis:	06.06.2022

TERMS OF REFERENCE:

Initial date for research work: *(the name of the object of research or design; performance or load; mode of operation (continuous, periodic, cyclic, etc.); type of raw material or material of the product; requirements for the product, product or process; special requirements to the features of the operation of the object or product in terms of operational safety, environmental impact, energy costs; economic analysis, etc.)*	1. Production of non-carrier added Lu-177 by indirect method. 2. Separate Lu from Yb targets by cementation method 3. Purification of Lu from Yb target and Mercury cathode 4. Radiochemical assessment Neutron Activation Analysis 5. Analyze data by HPGe detector
List of the issues to be investigated, designed and developed *(analytical review of literary sources with the purpose to study global scientific and technological achievements in the target field, formulation of the research purpose, design, construction, determination of the procedure for research, design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).*	– To analysis optimal possibility of producing Lu-177 by indirect route at research reactor IRT-T for purpose of nuclear medicine. – Production of ^{177}Lu by indirect method; – Determination theoretical production yield of Lu-177; – Methodology - Preparation & Irradiation of Yb_2O_3, Lu_2O_3 - Target processing and preparation of tracers - Separation of Lu/Yb cementation methods - Purification by cation exchange chromatography using Lewatit MonoPlus T214 resin - Radiochemical assessment by NAA and HPGe detector
List of graphic material *(with an exact indication of mandatory drawings)*	
Advisors to the sections of the Master Thesis	

(with indication of sections)	
Section	**Advisor**
One: Introduction	S.N. Tichenko /I.A. Ushakov
Two: Literature review	S.N. Tichenko /I.A. Ushakov
Three: Theoretical Calculations	S.N. Tichenko /I.A. Ushakov
Four: Experiment Method	S.N. Tichenko /I.A. Ushakov
Five: Financial management, resource efficiency and conservation	Luibov Y. Spicyna
Six: Social Responsibilities	Yuriy V. Perederin
Seven: Results and Discussions	I.A. Ushakov
Eight: Conclusions	I.A. Ushakov

Date of issuance of the assignment for Master Thesis completion according to the schedule	14.03.2022

Assignment issued by a scientific supervisor / advisor (if any):

Position	Full name	Academic degree, academic status	Signature	Date
Associate professor	I.A. Ushakov			
Associate professor	S.N. Timchenko	PhD		

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM0M	Mere Paballo Angelah		14.03.2022

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School of Nuclear Science & Engineering
Field of training (specialty): 14.04.02 Nuclear Science and Technology
Specialization: Nuclear medicine
Level of education: Master degree program
Nuclear Fuel Cycle Division

Period of completion: spring semester 2021/2022 academic year

Form of presenting the work:

Master Thesis

SCHEDULED ASSESSMENT CALENDAR
for the Master Thesis completion

Deadline for completion of Master's Graduation Thesis:	06.06.2022

Assessment date	**Title of section (module) / type of work (research)**	**Maximum score for the section (module)**
14.03.2022	*Development of technical assignment*	
20.03.2022	*Literature review on methods of obtaining of Lu/Yb by cementation process*	
25.03.2022	*Experimental methods for target irradiation and processing, separation and purification of Lu/Yb*	
06. 04.2022	*Analysis of acquired Lu and Yb peaks by HPGe detector Radiochemical assessment by NAA.*	
06.05.2022	*The analysis of obtained results and writing the dissertation full report*	
22.05.2022	*The completion of thesis work*	

COMPILED BY:
Scientific supervisor:

Position	**Full name**	**Academic degree, academic status**	**Signature**	**Date**
Associate Professor	Timchenko Sergey Nikolaevich	PhD		

APPROVED BY:

Program Director	**Full name**	**Academic degree, academic status**	**Signature**	**Date**
Nuclear medicine	Vera V. Verkhoturova	PhD		

ASSIGNMENT FOR THE DIPLOMA PROJECT SECTION
«FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING»

Student:

Group	Name
0AM0M	Mere Paballo Angelah

School	**Инженерная школа ядерных технологий / School of nuclear technology engineering**	**Department**	**ОЯТЦ / Division of Nuclear Fuel Cycle**
Educational level	Master degree	**Specialization**	14.04.02 Ядерные физика и технологии / Nuclear Physics and Technology

Initial data for the section "Financial Management, Resource Efficiency and Resource Saving":	
1. *The cost of scientific research resources: material, technical, energy, financial, informational and human*	*Budget of research not higher than 400 000 rubles, salaries of executors not higher than 150 000 rubles*
2. *Norms and standards for spending resources*	*Consultant's salary is 52 000 rubles per month; executor's salary is 50 000 rubles per month*
3. *The system of taxation used, tax rates, volumes of payments, discounts and loans*	*According to clause 3 of subclause 16 of Art. 149 of the Tax Code of the Russian Federation, this project is not subject to taxation. Based on Chapter 34 of the Tax Code of the Russian Federation, since 2016, the rate of 30.2% of the wage fund has been used to calculate contributions to extra-budgetary funds.*
Problems to research, calculate and describe:	
1. *Assessment of the commercial potential of engineering solutions*	*Comparison of the possible engineer solutions*
2. *Planning of research and constructing process and making schedule for all periods of the project*	*Calendar plan of the project*
3. *Requirement for investments*	*Cost calculation*
4. *Budgeting an engineering project*	*Creation of the project budget*
5. *Calculation of resource, financial, social, budgetary efficiency of an engineering project and potential risks*	*List of resource requirements*
Graphic materials	
1. *«Portrait» of the consumer* 2. *Competitive power of the project* 3. *SWOT matrix* 4. *Assessment of the prospects of a new product* 5. *Plan of investments. The budget for scientific and technical research* 6. *Project Efficiency indicators* 7. *Project risks*	

Assignment date	

Consultant:

Position	Name	Academic degree	Signature	Date
Associate Professor Division for Social Sciences and Humanities	Spicyna Lubov Yurievna	PhD		

School of Core Engineering Education				

Student:

Group	Name	Signature	Date
0AM0M	Mere Paballo Angelah		

Form of the assignment for the section "Social responsibility"

ASSIGNMENT FOR THE SECTION "SOCIAL RESPONSIBILITY"

To the student:

Group	Full name
0AM0M	Mere Paballo Angelah

School	Nuclear science and Engineering	**Department**	Nuclear Science and Technology
Degree	Masters	**Specialization**	Nuclear medicine

Input data to the "social responsibility":	
1. Describe workplace (work area) for occurrence of:	- *Environmentally harmful factors (microclimate, illumination, noise, vibration, electromagnetic fields, ionizing radiation).* - *Environment factors that are hazardous (electrical, fire and explosive nature).*
2. Acquaintance and selection of legislative and normative documents on the topic	- *When working on a computer labor protection standards are all important considerations.* - *electrical safety,* - *fire and explosion safety,* - *Radiation protection.*
The list of subjects to study, design and develop:	
1. Analysis of the identified harmful factors of the environment in the following sequence:	- *The impact of the element on the human body.* - *The reduction of allowed standards to the needed dimensions (with reference to the relevant normative and technical document).* - *Solutions that have been proposed (collective and individual).*
2. Analysis of identified hazards of the environment:	- *Electrical safety (including static electricity, protective equipment).* - *Fire and explosion safety are two of the most important factors to consider (causes,*

	preventive measures,. Primary fire extinguishing agents).

Date of issue of the task for the section according to the schedule	14.03.2022

Task issued by consultant:

Position	**Full name**	**Scientific degree, rank**	**Signature**	**Date**
Senior lecturer	Yuriy V. Perederin	PhD		

The task was accepted by the student:

Group	**Full name**	**Signature**	**date**
0AM0M	Mere Paballo Angelah		14.03.2022

_____

Abstract

The master’s dissertation consists of 175 pages; 35 figures; 54 tables; and 108 references.

N.C.A. Lu-177 was produced by indirect method at Nuclear Research Reactor IRT-T by irradiating Yb-176 targets at thermal neutron flux of 2 x 10^{13}n.cm^{-2}.s^{-1}. Aim of the research was to carry out chemical separation by cementation methods followed by purification process utilizing Lewatit MonoPlus T214 cation exchange resin, analyze data obtained by Neutron Activation analysis methods using HPGe detector. The final product is beneficial for clinical measurements in the territory of Tomsk, Russia"

Key words.
Cancer. Radioisotope Production. Cation Exchange Resin. n.c.a Lu-177. Indirect Method. Cementation method. Specific Activity. Radionuclide Purity. Cation Exchange Resin.

Abbreviations

N. C. A	Non-carrier added
C.F	Carrier-free
C. A	Carrier added
FDA	Food and Drug Administration (FDA)
Yb	Ytterbium
Yb2O3	Ytterbium Oxide
Lu2O3	Lutetium Oxide
Lu	Lutetium
NAA	Neutron Activation Analysis
HPGe	Hyper Pure Germanium Detector
SA	Specific Activity
SPECT	Single-photon emission computed tomography
PET	Positron emission tomography
CT	Computer Tomography
DOTATATE	[DOTA0,Tyr3]octreotate
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
SSRTs	Somatostatin receptors
NETs	Neuroendocrine tumors
EOB	End of bombardment
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
WHO	World Health Organization
EDTA	Ethylene diamine tetra-acetic acid
EDTMP	Ethylene diamine tetra methylene phosphonic acid
GMP	Good Manufacturing Practice
GEP-NETs	Gastro-enteropancreatic neuroendocrine tumors

18F-FDG	18F-fluorodeoxyglucose
TRT	Targeted Radionuclide Therapy
PRRT	Peptide Receptor Radionuclide Therapy
^{177}Lu-DOTATATE	^{177}Lu-DOTA-Tyr3-octreotate lutetium oxodotreotide LU-177
^{177}Lu-PSMA-617	^{177}Lu-prostate-specific membrane antigen-617
PSMA	Prostate-specific membrane antigen

Table of Contents

Chapter 1

1. Introduction

The World Health Organization defines cancer is a global disease that affects human tissues or organs and is caused by the uncontrolled growth of abnormal cells in any part of the human body. Cancer is known as a disease that is quite tricky to diagnose at an early stage [1]. At low doses, ionizing radiation can be used to acquire details of patient's diseased organs, identify early stages of cancer such as multiple myeloma, osteolytic lesions, bone fractures and so on, by means of radiographs or CT-scans and MRI; this concept is known as diagnostic radiology. Other diagnostic methods are nuclear medicine tests which utilizes the use of medical radioisotope to study the human organs, malignant diseases [2].

Nuclear medicine, which is a medical specialty that is part of radiology that helps to diagnose and treat diseases, utilizes prescribed dosages of radioactive sources either administered orally or intravenously to patients to assess organ function, identify anomalies, and treat diseases such as active infections. A wide range of diagnostic medical radioisotopes were reported by Grupen et.al [3], amongst them, is technicium-99m which is used in thyroid scan prior ^{131}I treatment for thyroid cancer [4], ^{18}F-FDG for PET/CT scan which was reported to have shown excellent diagnostic performance in the identification of soft-tissue, nodal, and visceral metastases during initial staging and follow-up, ^{90}Yttrium used to treat cancer, especially non-Hodgkin's lymphoma and liver cancer, ^{131}Iodine, ^{153}samarium and ^{32}phosphorus are also used in radiotherapy and to name few, that; ^{131}Cesium, ^{103}palladium (^{103}Pd) and ^{223}radium are used in special cases [5].

Upon diagnosis, follows treatment which can either be chemotherapy, surgery and/or radiation therapy or combination of these treatment modalities. Radiation therapy is a

cancer treatment that uses ionizing radiation such as x-rays, photons, neutrons and other source of radiation to destroy cancer cells and reduce tumors by disrupting the DNA of the cells, preventing them from growing and multiplying.

There are different types of radiation therapy such as external beam radiation therapy (EBRT) [6] where the radiation source is delivered into the body directly to a tumor by advanced treatment machines such medical linear accelerators, or internal radiation therapy, in which the radioactive source is placed near cancerous cells by brachytherapy. Targeted radionuclide therapy (TRT) or peptide receptor radionuclide therapy (PRRT) [7] are also form of internal systematic radiation therapy as it employs a biological molecule labelled with a medical radioisotope synthesized into a radiopharmaceutical to deliver a radiation dose to the targeted diseased organs [8].

Radioisotope production is one of the fastest-growing sectors, owing to its impact on medicine, particularly cancer. Produced radioisotopes by means of technologies such as particle accelerator, cyclotrons or nuclear reactors etc. must meet clinical requirements such as having highest specific activity, free of impurities i.e., be carrier-free, and should not have toxicity. One of the characteristics of radiopharmaceuticals is that they must undergo decay with a unique half-life and decay mode, so it can be eliminated from the body with an effective half life time approximately equaling the examination time to prevent subsequent exposure to the body [8]. Long half-lives are not useful in nuclear medicine, even for therapy, because the delivered dose is governed by the patient's total radiation exposure. The dose attributed outside the window for imaging or therapy needs to be reduced, very long half-lives will deliver the majority of the dose outside that window [9].

A radionuclide of interest in this paper is ^{177}Lutetium which is radioligand therapy that is still radiolabeled as ^{177}Lu-DOTATATE as a treatment of GEP-NETs, ^{177}Lu-PSMA-

617 for exploiting prostate-specific membrane antigen (PSMA), a receptor significantly activated on prostate cancer cells [10]. Medical radioisotope ^{177}Lu can be produced by cyclotron and at the nuclear reactor by direct method from irradiating Lu-176 targets or indirect method prepared from ^{176}ytterbium which is irradiated and transformed into ^{177}Yb, which rapidly returns to ^{177}Lu [11], [12].

1.1. Targeted Radionuclide Therapy: Lu-177 in nuclear medicine

Targeted radionuclide therapy (TRT) involves the use of radiopharmaceuticals designed to specifically target cancer cells. These radiopharmaceuticals have rapidly grown in popularity, with agents such as ^{177}Lu-DOTATATE, ^{177}Lu-PSMA, which targets PSMA, is also emerging as an attractive strategy for metastatic castration-resistant prostate cancer, with large late-phase clinical trials under way [13]. In contrast to conventional radiation therapy, PRRT/ TRT therapies are categorized with the concepts of theragnostic – which is a combination of diagnostic and therapeutic treatment, a comparison of with conventional radiation therapy is shown in figure 1.1 [14].

Peptide receptor radionuclide therapy (PRRT) is a type of site-directed targeted therapeutic strategy that specifically uses a cell-targeting protein (or peptide), identical to the natural circulating hormone somatostatin, mixed with a small amount of radioactive material, or radionuclide, to create a radiopeptide, a unique sort of radiopharmaceutical. This radiopeptide travels and binds to neuroendocrine tumor cells after the intravascular administration to deliver cytotoxic radiation to tumor cells. PRRT is a therapeutic option for gastro-enteropancreatic neuroendocrine tumors (GEP-NETs) that has scattered throughout the human body, Neuroendocrine tumors (NETs) that develops in any organ or tissue [15].

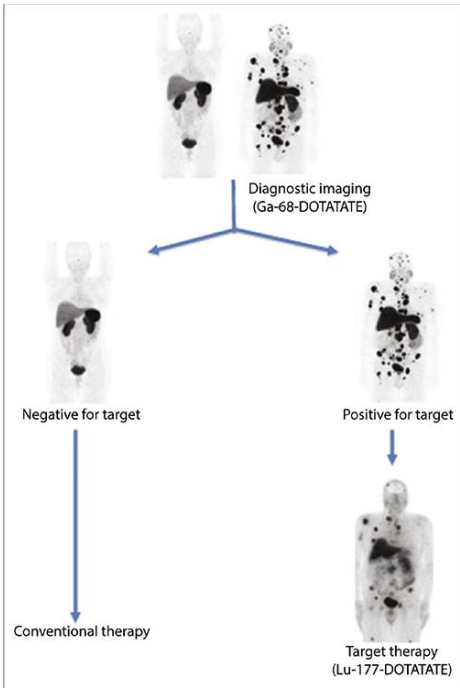


Figure 1.1. Targeted radionuclide therapy demonstrating how theragnostic systems combine diagnostic imaging (Ga-68-DOTATATE PET/CT) to detect the presence of a molecular target (somatostatin receptors) in each patient. A patient who is found to be positive for a molecular target is selected for therapeutic intervention, in this case Lu-177-DOTATATE [14].

The approval of ^{177}Lutetium-DOTATATE for clinical use by the United State Food and Drug Administration (FDA) in January 2018 for the treatment of a type of GEP-NETs was supported by the findings in the open-label phase III NETTER-1 trial wherein the two clinical trial study incorporated about 229 patients that were affected with the somatostatin receptor-positive GEP-NET that had advanced. In this clinical trial:

- Options involved 116 patients who received the treatment of ^{177}Lutetium-DOTATATE at 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations with drug octreotide long-acting repeatable (LAR) 30 mg by intramuscular injection every 4 weeks and 113 patients received high-dose long-acting octreotide at 60 mg by intramuscular injection every 4 weeks. Amongst other objectives in this study was determining the period progression-free survival i.e., the period during which tumors did not grow after treatment and it was found that progression-free survival

was longer for patients taking treatment with octreotide compared to patients who received octreotide alone. In the second clinical study, 1,214 patients with the same conditions were given ^{177}Lutetium-DOTATATE, observations of complete or partial tumor shrinkage was reported in 16% of a subset of 360 patients, evaluations were made by the FDA [16]–[18].

- Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile still to be under investigations and some reports have been published [19]–[21] as well as prescription information pack [22]. The method of administrating Lutathera has been widely adopted as Asti M. et.al [23] reported and figure 1.2 is showing a gravity infusion method tubing connection scheme for Lutathera administration.

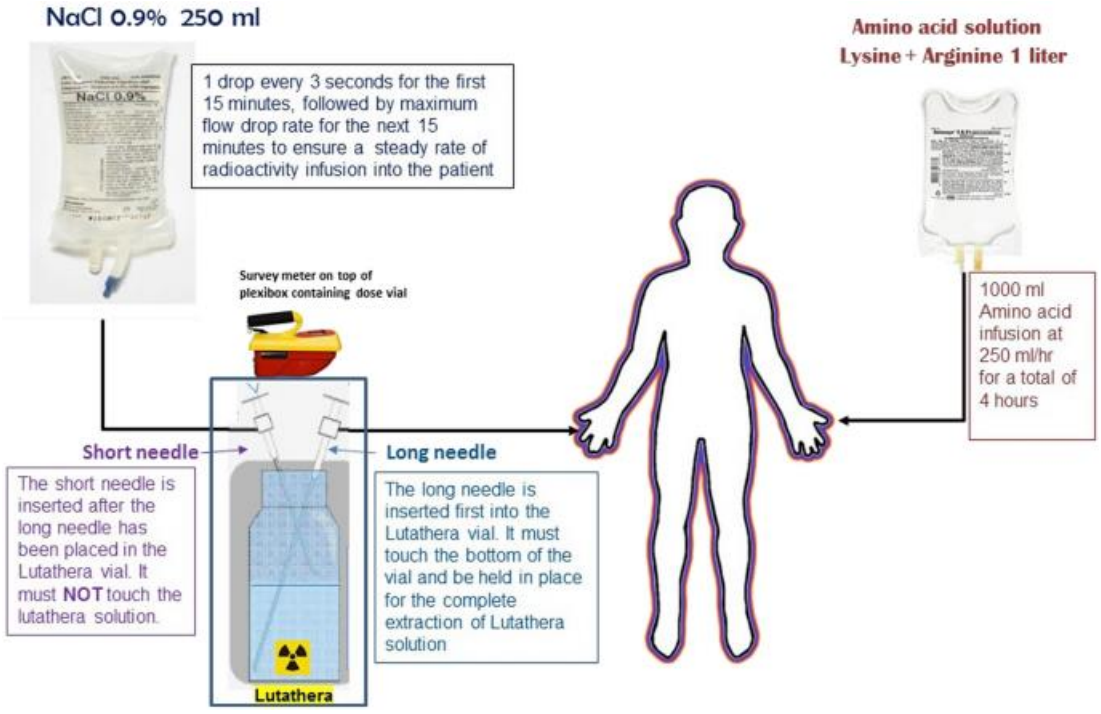


Figure 1.2. Gravity infusion method tubing connection scheme for ^{177}Lutetium-DOTATATE administration [23].

1.1. Problem statement

Radioisotope Lu-177 production process by using thermal neutrons in a nuclear reactor is mainly preferred and explored for medical applications following the most commonly routes adopted worldwide which are “direct” and “indirect” method; or by high energy particle accelerators (cyclotrons) – less explored route.

By the direct method, Lu-177 is produced by irradiating enriched ^{176}Lu targets wherein the results may contain long lived radioisotope Lu-177m and indirect method offers the possibility to obtain non-carrier added Lu-177 by irradiating ^{176}Yb targets using enriched ^{176}Yb; however, this process has drawbacks of needing chemical separation methods for which some may not be suitable or in some cases it may be expensive.

The choice of natural or enriched target used for irradiation depending upon the type of primary impurities they may pose, their abundance, neutron activation cross section and half-life of the radionuclidic impurity formed, formation of the radionuclidic impurity must be minimized or can be completely eliminated by proper choice of irradiation parameters and post irradiation cooling of the permit decay of short-lived radionuclidic impurity. At a nuclear reactor, the choice of high purity target materials, natural or enriched is important as it may contribute start up chemical impurities, particularly when the elements of the same group have to be separated in case of Lu and Yb as they are lanthanides, they put a limitation on the purity of the final radioisotope product [12].

In this paper, non-carrier added Lu-177 will be extensively discussed in the other sections, and for meeting the medical application requirements, separation process must take place where firstly, radiochemical species are separated based on differences in

chemical characteristics by cementation methods, followed by purification process by cation exchange chromatography.

1.2. Aims and Objectives

- Produce non-carrier added Lu-177 by indirect method.
- Separate Lu from Yb targets by cementation method
- Prepare cation exchange column using Lewatit MonoPlus T215 resin for purification of Lu from Yb target and Mercury cathode
- Analyze data by HPGe detector
- Analyze the chemical impurities in obtained Lu-177 using NAA
- Determine of radionuclide chemical purity of Lu-177, separation parameters, theoretical activity of Lu-177
- Asses of n.c.a $^{177}LuCl_3$ for radiolabeling for application in medicine

1.3. Goal:

The goal of this research is to achieve optimum production methods for Lutecitium-177 radioisotope for nuclear medicine by cementation process at the nuclear research reactor IRT-T

1.4. Working hypothesis achievable specific activity and Irradiation yield

Non-carrier added Lu-177 can be produced at a TBq level through irradiation of massive 176Yb targets. High SA can be achieved by using highly enriched ^{176}Yb target material, thus avoiding cold Lu and ^{177m}Lu and, choice of separation method based on cementation as method of choice for the separation of the two adjacent elements because it is a very simple operation and not time-consuming method can easily separate targets

with big masses. Upon this process is a purification process by cation exchange chromatography with Lewatit Monoplus TP 214 ion exchange resin.

1.5. Research Relevance

Production of radiopharmaceutical Lu-177 is one of the developing and growing medical radioisotope in nuclear medicine, diagnosis, therapy, theragnostic applications. With the approval of this radioisotope by the FDA in 2018 [22], this has paved a way for research in this field and increasingly in education, research, radiochemistry (production of radioisotope), cancer research institute, radiobiology research in biodistribution patterns of Lu-177 before clinical trials. This research is relevant in the field mentioned above, in particular to diagnostic, Lu-177 can be used to image biodistribution in vivo using a PET/SPECT-CT, gamma camera, Imagine fusion: CT, MRI. Lu-177 treatments: Radiopeptide drug used in PRRT: Lutetium-177 DOTATATE. Lutetium-177-PSMA therapy is amongst the best methods for treating late-stage prostate cancer with metastatic or treatment-resistant tumors. Lu-177-PRRT using Lu-177 DOTATATE; works in much the same way, but is more effective in treating advanced stage neuroendocrine tumors.

Chapter 2: Literature Review

Introduction

Radionuclide manufacturing is an ongoing process that is subject to continual study and development. Finding the most elegant approach to produce a radionuclide entails not only identifying the optimal reaction pathway, but also taking into account every step of production, from the generation of target materials to radionuclide separation and target recycling. Nuclear reactors and particle accelerators are almost entirely used to produce radionuclides needed in nuclear medicine.

1.6. Production of radionuclides

The primary distinction between the two techniques of production is that nuclear reactors bombard targets with neutrons, whereas particle accelerators bombard targets with a variety of charged particles (e.g., hydride ions, protons, deuterons, and alpha particles). Other important factors in nuclear reactor production are the following [24], [25]:

- Neutrons energy as well as neutron flux,
- Target material characteristics and the intended reaction's activation cross-section.

Nuclear reactors produce neutrons as a result of nuclear fission processes, nuclear fusion and/or neutron activation. Neutron activation reactions are (n, γ) or (n,α) and (n,γ) is the most common, thus producing isotopes of the target material, for example [24], [25];

$$^{124}Xe + (n,\gamma) \; ^{125}Xe \xrightarrow[(\mathrm{T1/2=17hr})]{EC\ or\ BetaPlus} \; ^{125}I$$

Nuclear reactor-produced radionuclides are usually neutron-rich, and thus decay mainly by β^- decay by the nuclear reaction:

$$ {}^{A}_{Z}\mathrm{X} \rightarrow {}^{A}_{Z+1}\mathrm{X}' + {}^{0}_{-1}\beta + \text{antineutrino} $$

By Nuclear fission, the nucleus of an atom is split in this process, resulting in the nuclei of lighter atoms and neutrons. The mass of the produced products is lower than the original mass. For example, production of Iodine-131 from irradiation of TeO_2 enriched with Te-130 [24], [26].

$$ {}^{130}_{52}Te + {}^{1}_{0}n \rightarrow {}^{131}_{52}Mo\ (+\gamma) \rightarrow {}^{131}_{53}I + {}^{0}_{-1}\beta + \gamma $$

(t1/2 = 25 mins) (t1/2 = 8.02 days)

Iodine-131 in the form of sodium iodide (NaI) or can also be attached to a pharmaceutical to form meta-iodobenzylguanidine (MIBG). The radioactive isotope of iodine (T1/2=16.9), is used for brachytherapy purposes, it has an advantage of treating several kinds of cancer: prostate, lung, eye, brain [27].

Particle accelerators. Cyclotrons

Radionuclides can be produced in cyclotrons (or other particle accelerators) by accelerating heavy charged particles (e.g. p,α, d) to bombard stable nuclei. In cyclotron, these radioactive isotopes can be produced 18F, ^{67}Ga, ^{123}I, ^{57}Co, ^{201}Tl. Example of nuclear reactions [24], [28].

$$ {}^{124}Xe + (p,2n)\ {}^{123}Cs \xrightarrow[(\mathrm{T1/2}\ \sim 1\mathrm{sec})]{EC\ or\ BetaPlus} {}^{123}Xe \xrightarrow[(\mathrm{T1/2=2hr})]{EC} {}^{123}I $$

Radionuclide generator systems.

A radionuclide generator is yet another source of producing radionuclides for medicinal applications. In a radionuclide generator, A resin-bound, longer-lived parent radionuclide decays producing a chemically distinct daughter nuclide, which may then be readily separated from the parent. In nuclear medicine, the 99Mo/99mTc generator is the most commonly available. Nuclear reaction is shown below [25], [26]:

$$^{99}_{42}Mo \xrightarrow{\beta,\gamma} {}^{99m}_{43}Tc \rightarrow {}^{99}_{43}Tc + \gamma$$

t1/2 = 66 hr (t1/2 = 6 hr) (t1/2 = 2.1x105 yr)

The γ is weak and is the detected in the scan

When determining the radioisotope yield, the following parameters are taken into consideration:

Activity of radionuclide and targets.

Activity, A, is the term used to measure the decay rate of a radionuclide. Activity is measured in Curie (Ci) = 3.7 x 10^{10} dps Becquerel (Bq) = 1 dps, Becquerel (Bq) = 1 dps 1 Ci = 3.7 x 10^{10} Bq

Activity, A = λ N

The activity of a sample is based on the total number of radioactive atoms, N, and the probability of each atom undergoing radioactive decay.

$$\lambda = 0.693 / T ½$$

Units of λ are 1/time (1/sec, sec-1 or per second)

The decay constant, λ, represents the probability that a radioactive atom will decay and is is proportional to nuclide's half-life. Half-life is described as the time it takes for the amount of radioactive material to decrease by one half [26].

$$T½ = 0.693/ \lambda$$

Radioactive decay

$$\frac{dN'}{dt} = \lambda N$$

$$N(t) = N_0 e^{-\lambda t}$$

Multiplying both sides by decay constant, λ,

$\lambda N(t) = N_0 e^{-\lambda t}$, then recall A = λN to get activity.

Radioactive Activity decay is then given by

$$A(t) = A_0 \cdot e^{-\lambda t}$$

Another important term to discuss when producing radioisotopes is specific activity, which is the activity per unit mass given by the formula. Specific activity has the following terms,

- Atoms per Gram. This is the number of atoms of a radionuclide in one gram. It is defined by

$$N = \frac{6.02 \times 10^{23}\ atoms/mole}{A_W\ g/mol}$$

- Decay constant, λ = 0.693 / T ½ (hr., sec)

Therefore, *Specific activity (S_A)* can de denoted as:

$$SA = \lambda \cdot N$$

$$= \lambda \cdot 6.02 \times 10^{23} / A_W \text{ (dps. gram}^{-1}\text{)}$$

Typical units: Ci/kg or Bq/g

Determination of radioisotope yield

When a target is exposed to radiation in a reactor, the resultant radioisotope begins to decay with its own half-life, allowing the activation per second net growth rate of active atoms to be calculated [25]:

$$\frac{dN'}{dt} = \phi \cdot \sigma_{act} \cdot N_T - \lambda N'$$

where $\lambda N'$ indicates the decay rate of product nucleus, where N_T is the total number of atoms present in target, ϕ is neutron flux, σ_{act} is activation cross-section, N' the number of activated atoms, A is atomic weight of the target [26].

Determination of radionuclidic purity

Therapeutic radionuclides require a high level of radionuclidic and chemical purity. During the labeling of a radiopharmaceutical, impurities of other chemical elements might compete with the radioisotope for binding sites or ligands, reducing the effectiveness of the procedure. The chemical purity must also meet the in vivo application standards. The inclusion of radionuclidic impurities in a patient's body is an unneeded burden, and long-lived impurities impede waste disposal [26], [29], [30].

Choice of target material

When choosing an irradiation target material in a reactor, unstable or flammable substances should not be irradiated in the reactor. To facilitate post-irradiation processing, the target should be in chemically acceptable state such as oxides. Mercury in its elemental form is not allowed to be irradiated in many reactors along with the majority of reactor components are composed of aluminum, which can produce an amalgam when aluminum comes into contact with mercury. Under irradiation, targets should remain stable, it should not disintegrate into gaseous products when exposed to irradiation. Irradiation of generally unstable compounds, such as hydrocarbons, is only authorized under very strict circumstances. To avoid the creation of undesired radionuclides, high purity targets should

be irradiated. Enriched target materials allow radioisotopes with higher specific activity to be produced [26] .

Target encapsulation

Prior to delivering target materials into the reactor, they must be appropriately enclosed in appropriate containers. The encapsulation material and method will be determined by a variety of factors, including the physical form of the target (solid, liquid, or gas), the target's characteristics, the duration of irradiation, the design of the irradiation assembly in the reactor, the type of coolant used in the reactor, the proposed post-irradiation handling, and the radioisotope's intended use. Aluminum, zircaloy, and stainless steel are the most frequent encapsulating materials. The bulk of targets, however, are encased in aluminum capsules. The following are some of the reasons why aluminum was chosen as the material for making irradiation capsules:

- The cross-section of absorption is small (aluminum is essentially translucent to neutrons) because radioisotopes generated in aluminum capsules have a limited half-life, post-irradiation treatment and disposal are simple.
- Because of the target's high thermal conductivity, heat created in the target may quickly be transferred to the coolant.
- By cold welding a cover to the container with the desired material inside, an air/water proof container may be created. This has the benefit of preventing oxidation and degradation of the targets by not exposing them to extreme heat capsules that have been cold welded [26].

Target processing

- Irradiation targets of choice are produced in chloride form solutions in a hot cell that is appropriately insulated for processing the irradiated target [26].

Neutron Activation analysis and impurity detection.

During nuclear activation reaction, target interact with object subjected to particles they bombardment with. Targets used in nuclear research in most cases are made of the enriched isotopes, they contain different various dimensions, thickness, physical (solid, liquid, gaseous) and chemical (elemental, compound or alloys) forms. Processing of these targets and product of radioisotope obtained for detection of impurities by gamma spectrometry and NAA is very essential in determination of radionuclidic purity[31].

Dispensing, testing and quality control/assurance

Purity of radionuclides and radionuclide identification of the 177Lu product is examined using an HPGe detection device and gamma ray spectrometry. The γ-spectrometry with germanium detectors is a non-destructive technique which is extensively used to determine the radioactive concentration of natural and artificial radionuclides in the environment [26].

Radiochemical purity.

The target material's radionuclidic purity must be more than 99 percent. The proportion of total radioactivity in a sample contained in the desired chemical form is analyzed by using a calibrated well type ionization chamber, the radioactivity of the target in the ampoule is determined. The purpose of γ-ray spectroscopy in NAA is for measuring the energies and intensities of the photons emitted by the radionuclides. In general, a γ-ray is emitted from

the sample and enters the detector, where it goes through a number of interactions ultimately resulting in the ionization of the germanium atoms in the detector crystal [26].

1.7. Nuclear Reactor Production of Lu-177

Lutecium -177 can be produced via two different pathways in the reactor is using thermal neutrons to obtain high specific activity. These methods are based on neutron irradiation of either enriched ^{176}Lu (direct production) or ^{176}Yb (indirect route) using $^{176}Lu_2O_3$ or $^{176}Yb_2O_3$ as target material. Figure 2.1 shows reaction pathways to produce lu-177. Other methods producing Lu-177 by cyclotron is discussed in section 2.5.

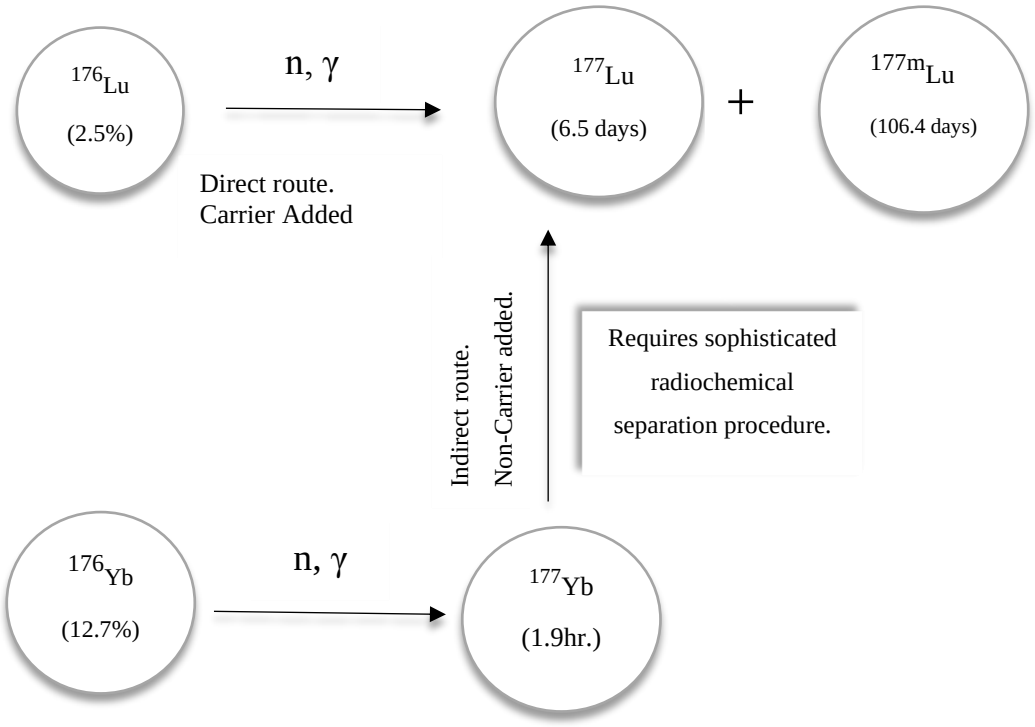


Figure 2.1. Lu-177 Production Methods at Nuclear Reactors.

1.8. Properties of Radionuclide Lutecium -177

Lutetium-177 is a rare earth metal in the lanthanide series containing 71 protons and 106 neutrons known to have β- and a γ-emissions with a physical half-life that is about 7 days, and as the most supported value by the Decay Data Evaluation project from 2004 is 6.647 days which is inline recent measurements of 6.7 days which decays to three excited states and the ground state of Hafnium-177 at the energy of 0.49 MeV by beta minus decay [32], [33].

The energy β energy of ^{177}Lu can be classified as "low" or "medium" to be recognized from β-emitters that has high energy such as ^{90}Y and ^{131}I and this characteristic is advantageous due to the penetration ability β-particles to be strongly distributed locally in tissue up to 0.23 mm thus allowing destructions of cancerous cells. Nuclear decay scheme is shown in figure 1.3. where emission of β-particles with reaches maximum energy, E_{max} of 497 keV which account to about 79.3%, 384 keV that is 9.1%, and 176 keV making up 12.2% leading to formation of ^{177}Hf. A simplified decay scheme is shown in figure 2.2. [6], [34], [35].

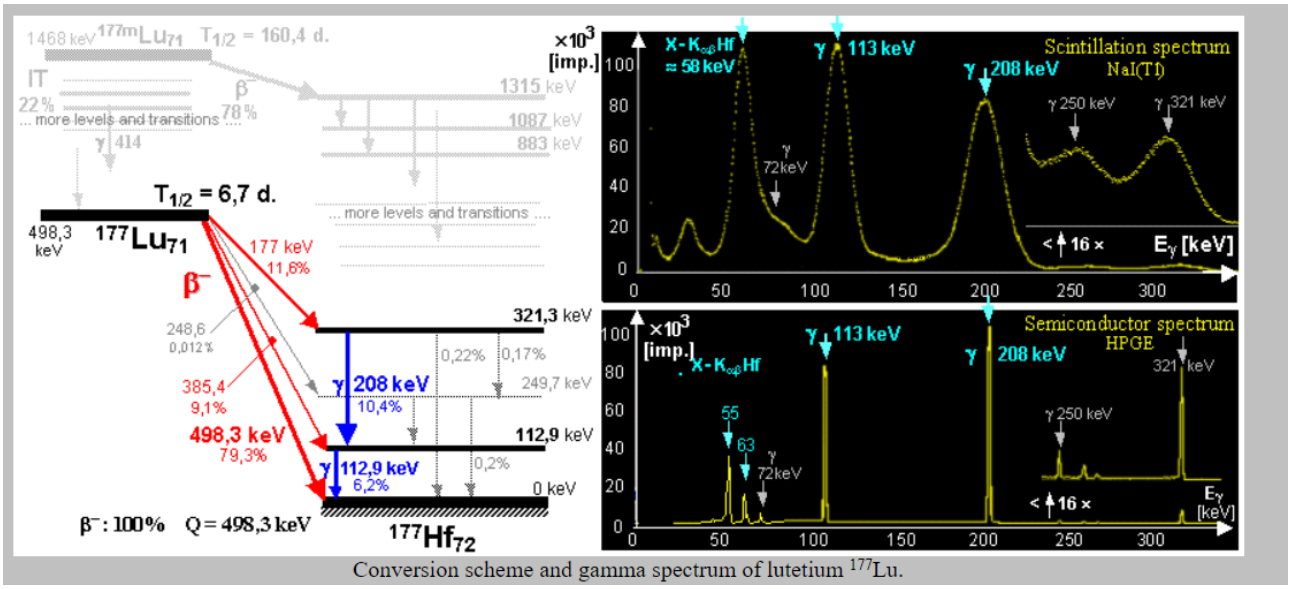


Figure 2.2. A simplified decay scheme which accounts for the major β−- particle and γ-photon emissions from 177Lu [6], [34], [35].

Other suitable radiotherapy applications involve the two main Lu-177 γ photons of 113 keV (~6.4%) and 208 keV (~11%) for nuclear imaging and localization invivo, post-therapy imaging where doctors can be able to see that radiation has been delivered to the intended areas of disease and also allows for response evaluation with subsequent cycles [36].

Additionally, Lu-177 is used for the treatment of advanced prostate cancer [37] when linked with molecules targeting the prostate specific antigen (PSA) and somatostatin expressing gastroenteropancreatic neuroendocrine tumors [38] and other clinical trial were carried out and reported by Hofman et.al and Tagawa ey.al respectively [39], [40].

1.9. Direct route production of Lu-177

With a reasonably high specific activity, ^{177}Lu can be generated directly by neutron capture on ^{176}Lu in nuclear reactors. By irradiation of a ^{176}Lu target, a long-lived isomer is co-produced by the competing ^{176}Lu (n, γ) ^{177m}Lu reaction which lowers the radionuclidic purity of ^{177}Lu preparations obtained and complicates the disposal of radioactive ^{177}Lu waste in hospitals [6]. This method of manufacturing necessitates the use of enriched target material since the natural abundance of ^{176}Lu is only 2.6%, Lu_2O_3 enriched in ^{176}Lu up to approx. 60–80% are commercially available A downside of this production process is that only carrier-added ^{177}Lu preparations can be obtained because stable ^{175},^{176}Lu isotopes (though burned-up to some extent) are found in the target[41]. High-flux reactors can attain the highest achievable specific activity, which is around 70% of the theoretical value [26], [42].

Target processing

- For processing the irradiated target, radioactive ^{177}Lu produced as $^{177}LuCl_3$ in HCl solution in a suitably shielded hot cell is required [26].

Impurity details.

The target decays for 3 days after irradiation for a change in activity of ^{176m}Lu (half-life 3.664 h) induced by the side reaction [26].

Requirements for the final product

The irradiation times necessary to reduce the creation of the long-lived ^{177m}Lu generated by the competing ^{176}Lu (n, γ)^{177m}Lu reaction might restrict the specific activity of lutetium-177 directly synthesized from enriched lutetium-176. The indirect approach yields the most radiochemically pure lutetium-177 for these reasons [26], [42]. A. Golabian et.al [43] exploring the feasibility of ^{177}Lu production at Isfahan Miniature neutron source reactors (MNSRs) by irradiation Lutetium (>99.98 chemical purity) with thermal neutron flux 5×10^{11}n.cm^{2}s^{-1} at 4 minutes irradiation time leading to maximum resulting in ^{177}Lu production of 723.5 mCi/g after 27 cycles. The two naturally occurring isotopes of lutetium are 175Lu (97.4 percent) and ^{176}Lu (2.6 percent), although only ^{175}Lu is actually "stable." With a half-life of $4x10^{10}$ years, ^{176}Lu decays through beta decay. The possible neutron capture reactions co-occurring during the irradiation of a Lu_2O_3 target are simplified in figure 1.5 (in black arrows) [44].

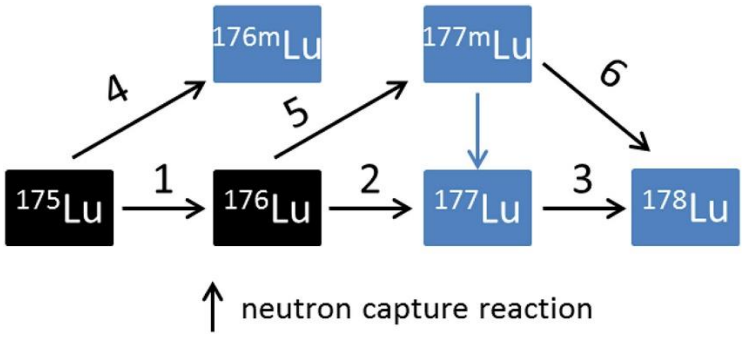


Figure 2.3. Neutron capture reaction affecting the ^{177m}Lu production.

The blue and black boxes indicate unstable and stable nuclides, respectively. Blue arrows indicate radioactive decay and black arrows indicate neutron capture reaction [44].

A nuclear reaction for the direct production of Lu -177 is given as:

$$^{176}Lu\ (n,\gamma) \rightarrow\ ^{177}Lu$$

By direct route production, ^{177}Lu absorbs neutron and produces $^{177/178}$Hf which result as the carrier in the target system (nuclear decay chain is shown in Figure 2.2). 177Lu's effectiveness is unaffected by the presence of $^{177/178}$Hf (IV) (III) The specific activity of -labeling processes is reduced when hafnium atoms accumulate [6], [12].

According to a study conducted at Oak Ridge National Laboratory, it is possible to achieve specific activities of 1,8502,405 GBq/mg (50–65 Ci/mg) by irradiation in high flux reactors like the HIFR reactor to obtain Lu-177 with specific activity values of >7401,110 GBq (20–30 Ci)/mg in medium flux reactors using an enriched 176Lu target up to approximately 60–80 percent [45], [46].

Direct production entails weighing 6 mg of natural Lu_2O_3 powder > 99.99 percent, isotopically enriched Lu_2O_3 (60.6 percent ^{176}Lu) and irradiating it for 7 days at a thermal neutron flux of $3x10^{13}n.cm^{-2}.s^{-1}$, the irradiation target was then dissolved in varying concentrations; for example, $^{Natural}Lu_2O_3$ in 1 M HCl gentle warming inside a lead-shielded plant, the resulting solution was evaporated to nearing dryness within a lead-shielded plant before being reconstituted in double distilled water. Following that, a known aliquot was extracted for radioactivity content and radionuclidic purity evaluation. The Enriched Lu_2O_3 was then dissolved in 0.1 M HCl, and a known aliquot of this solution was carefully evaporated to dryness in a quartz ampoule; the ampoule was then flame sealed and

irradiated after being placed within an aluminum container and irradiated under the same circumstances. Then chemical processing of the enriched Lu_2O_3 target resulted in approximately 110 TBq/g (3000 Ci/g) of ^{177}Lu, while natural Lu_2O_3 in ~ 4 TBq/g (108 Ci/g) of ^{177}Lu conditions [30], [45], [46]. M.R.A. Pillai [30] performed this study and compared these production logistics.

Obtaining Lu-177 at different neutron flux parameters are graphically shown in in figure 2.4 and summarized Table 2.1. Neutron flux values utilized in optimizing Lu-177m synthesis, as well as a graph showing 177mLu production as a product of irradiation duration at various thermal flux levels. The target consists of commercially available 84.44% ^{176}Lu enriched Lu_2O_3 [44].

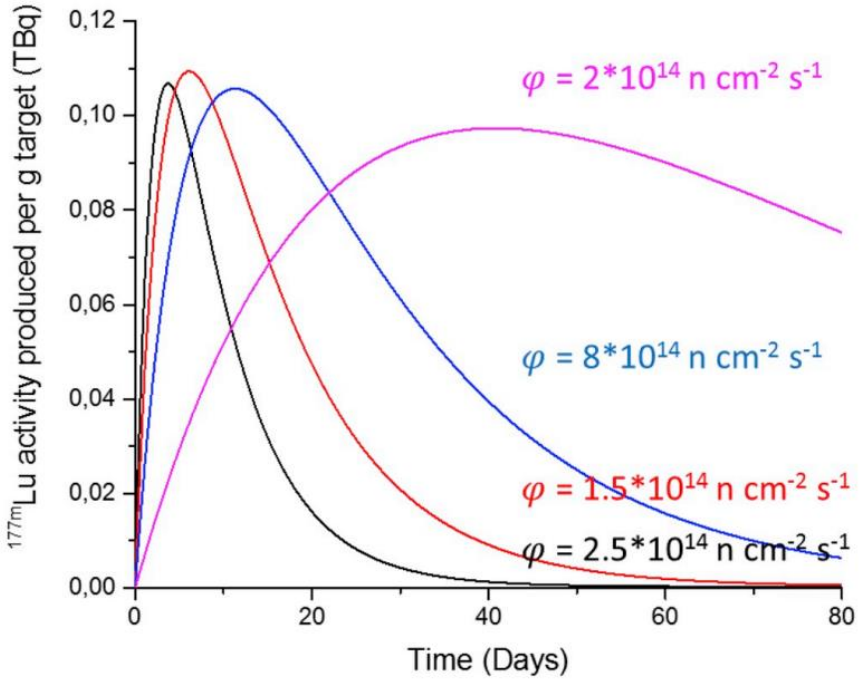


Figure 2.4. Production of Lu-177 at different neutron flux parameters [44].

Table 2.1 - Neutron flux values used to optimize ^{177m} production

Nuclear Reactor	Neutron flux ($n.cm^{-2}.s^{-1}$)
High- Flux Reactor (HFIR), ORNL, Oak Ridge, U.SA	Thermal flux: $2.5x10^{15}$ (In black)
High- Flux Reactor (ILL), Laue Langenivin Institute, Grenoble, France,	Thermal flux: $1.5x10^{15}$ (in red)
High- Flux Reactor (BRS), SCK.CEN, Mol, Belgium	Thermal flux: $2.1x10^{14}$ & Epithermal flux: $2.1x10^{14}$ (in Purple) Thermal flux: $8.4x10^{15}$ & Epithermal Flux: $8.4x10^{14}$ (in Blue)

1.10. Indirect Production of Lu-177

The medical radioisotope ^{177}Lu can be produced in a carrier-free through beta decay of ^{177}Yb produced by neutron capture on enriched ^{176}Yb targets using enriched $^{176}Yb_2O_3$ targets in a nuclear reactor forming short-lived intermediate radioisotope Yb-176 that has a half-life, $T_{½}$ = 1.9 h), which degenerate in the following manner [47]:

$$^{176}\text{Yb (n, γ) } ^{177}\text{Yb (}\beta^{-}\text{)} \rightarrow ^{177}\text{Lu}$$

The "indirect" technique is optimum for the preparation of ^{177}Lu without carrier as in the above shown two stage reaction with the stable isotope Yb-176. For the effective implementation of the scheme 176Yb → 177Lu, the initial ytterbium with the minimum content of ^{174}Yb is required, from which stable isotopes of lutetium are formed during the

irradiation and ^{177}Lu can be dissociated from the target material Yb-176 including intermediate radionuclide Yb-177 to obtain n.c. a^{177}Lu [47], [48].

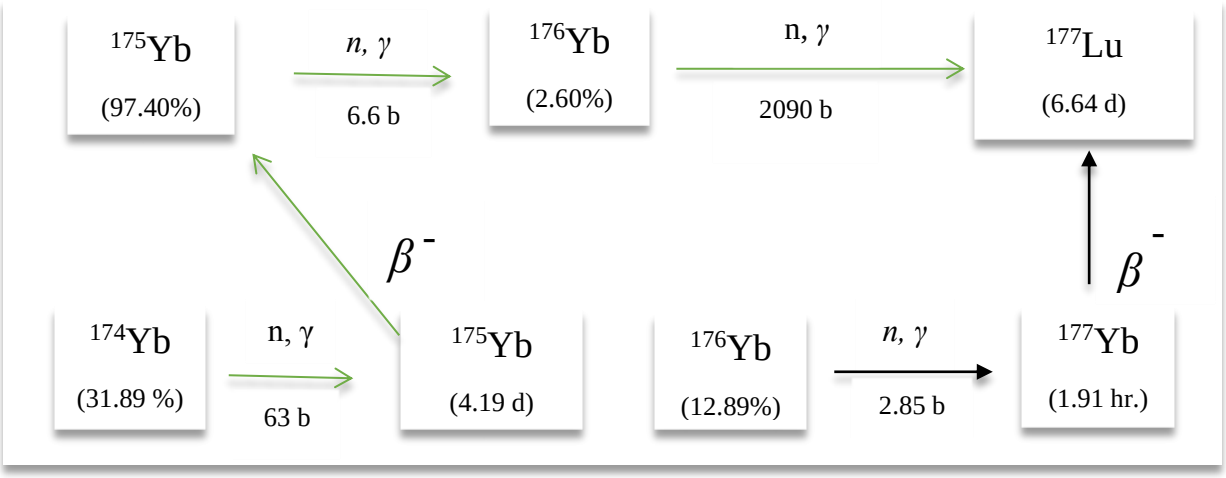


Figure 2.5. Nuclear reaction production of n.c.a Lu-177. Production can also be started by irradiating Yb-174 (green arrow)

In comparison to direct route, Dash.A et.al. [6] raised some concerns with direct route because the potential use of enriched ^{176}Lu targets is significant due to the quantity of ^{176}Lu natural abundance of 2.6 percent of ^{176}Lu in the non-enriched target. In comparison to the predicted SA value of 4.07 TBq (110 Ci)/mg, the specific activity of ^{177}Lu generated via direct route is typically equivalent to 740–1,110 GBq (20–30 Ci)/mg; however, this might imply that around 25% of the atoms are 177Lu and the remaining 75% are non-radioactive contaminating Lu-175/176 atoms [41]; hence, the greatest attainable SA that can be produced is through high-flux reactors to reach 70% of the theoretical value [6].

The theoretical specific activity of 'carrier-free (CF)'/ n.c.a ^{177}Lu is calculated from the following equation to determine the theoretical production yield, where λ is the decay constant, N_A is Avogadro's constant, M is the molar mass and $t_{1/2}$ is the half-life [6], [12];

$$SA_{CF} = \frac{\mathrm{dN}}{\mathrm{dT}} = \lambda \mathrm{N} = \frac{\ln(2) N_A}{T_{1/2} M}$$

$$SA_{CF} = \frac{0.693 \cdot 6.023 \cdot 10^{23}}{6.65 \cdot 24 \cdot 3600 \times 177}\,\text{Bq/g}$$

$$SA_{CF} = \frac{0.693 \cdot 6.023 \cdot 10^{20}}{(6.65 \cdot 24 \cdot 3600 \cdot 177}\,\text{Bq/mg} = 4.104\ \text{TBq/mg} = 110.91\text{Ci/mg}$$

The higher the specific activity that may be obtained, the greater the thermal neutron flux, reaction cross section, and target isotope enrichment [29], [41].

Bilewicz et al. used an indirect method to irradiate natural Yb_2O_3 with great chemical purity (99.999 percent). At the nuclear reactor Maria in Wierk, Poland, ^{177}Lu radiotracer was created by neutron irradiating a Lu_2O_3 target at a neutron flux of 3×10^{14} n.cm^{-2}. s^{-1} for 6 hours. Only 1 mg Yb remains in the solution after precipitation and separation of YbSO4; the specific activity of the 177Lu obtained was 700 MBq mg–1 from 50 mg of 176Yb irradiated target. A very successful and versatile approach for the separation of ^{177}Lu from irradiated Yb targets[6] was devised and the overall recovery of 177Lu was 73% [49].

By irradiating a variant of natural ytterbium ((12.7% ^{176}Yb, 31.8% ^{174}Yb, and 0.13% ^{174}Yb), Lebedev N et.al produced n.c.a ^{177}Lu from these targets. 200 mg of high chemical purity 99% ytterbium oxide Yb_2O_3 were bombarded for 6 hours at a neutron intensity of 2 x 10^{12} cm^{-2}s^{-1} in this study. They also irradiated 12.4 mg of 94.72% enriched ^{176}Yb as $^{176}Yb_2O_3$ for two days using a neutron source of 2 x 10^{14} n.cm^{-2}s^{-1}, yielding 8.1 GBq (activity) ^{177}Lu one day after EOB [50].

At the National Research Centre Kurchatov Institute ^{168}Yb and ^{176}Yb targets were irradiated at the IR-8 pool-type research reactor in a form of Yb $(NO_3)_3$ in quartz ampoules. The flux density and neutron fluence in the location of samples were (7.43 ± 0.64) x 10^{13}cm^{-2}.s^{-1} and (2.91 ± 0.28) x 10^{19}cm^{-2}.s^{-1}. the flux density and neutron fluence were (7.43 ± 0.64) x 10^{13}cm^{-2}.s^{-1} and (2.91 ± 0.28) x 10^{19}cm^{-2}.s^{-1}, respectively. Furthermore, within the sensitivity of the gamma-ray spectrometer, radionuclides ^{177}Lu, ^{169}Yb, and ^{175}Yb were detected in the composition of the sample of ^{176}Yb. The admixture of the long-lived

radionuclide ^{177m}Lu was not detected. the electrolysis and cementation were carried out in special-purpose electrolyzers, resulting in a 177Lu yield of 70%. The purification factor across four stages (10^5 –10^6) provides the possibility for the use of the obtained ^{177}Lu for the labeling of conjugates possessing an effect of targeted delivery[47].

The scientist worldwide apply different production parameters such as methods of obtaining Lu-177 (n.c.a/c.a), choice of target, irradiation times, different neutron flux conditions at nuclear reactor or cyclotron route at different, separation methods, target process etc. to production of n.c.a Lu177 gradually increasing. Since the approval of Lu-177 in medicine, different countries are investing various way to obtain this medical radioisotope that is applicable in clinical trials and overall therapy, diagnostics in nuclear medicine. At the IRT-T reactor, TPU scientists were the first in Russia to produce the first experimental batch, the university carried out internal audit and certification, after which the drugs were sent to the consume to synthesize radioisotope ^{177}Lu. The IRT-T research reactor has the ability to create ^{177}Lu both directly and indirectly. This demonstrates the relevance of TPU in the Tomsk Regions and throughout Russia, since it can create the ^{177}Lu radioisotope that may be delivered to hospitals for use in cancer therapy using nuclear medicine [51].

SAFARi-1 nuclear research reactor of the South African Nuclear Energy Corporation (NECSA)[26] is one of the countries of producing radioisotope ^{177}Lu, and commercially available from Nuclear Technology Production (NTP) group [52].

At SAFARI-1 reactor lu-177 was produced by irradiating 1 g of 99.56% enriched ^{176}Yb as Yb_2O_3 at a neutron flux of 5.94E14 n/cm2/s for 6–14 days and direct and indirect route was compared. By the direct route,100 μg of 82% enriched 176Lu processed in Lu $(NO_3)_3$ resulted in specific activities 105.3 and 100.2Ci/mg 6- and 14-day irradiation periods; and by indirect route and 19.5 and 27.8Ci/mg after two days' decay after EOB. After, 14 days decay specific activity decreased to 93.4 and 80.4Ci/mg for the indirect route

and 6.4 and 9.7Ci/mg for the direct route. In conclusion, specific activity for n.c.a ^{177}Lu at least 3.6 times higher than for c.a ^{177}Lu c.a. Furthermore, the 177mLu factor of 1E+04 was lower in 177Lu n.c.a.[53].

1.11. Other methods of producing Lu-177: Cyclotron

Cyclotron produced medical radioactive isotopes quite expensive compared to nuclear reactor methods. Alternative method of producing ^{177}Lu by cyclotron can be achieved cyclotron although this method is limited due to the costly operation [54]. This production route is relatively less explored because of the low batch yields of the process which is unsuitable to meet the clinical demands. Nevertheless, it is feasible approach to produce 177Lu of equivalent quality without depending on nuclear reactors to fulfil the requirements of research and development laboratories and academic institutions. The nuclear reaction routes are further compared in figure 2.6. by (A) cyclotron via ^{176}Yb (d, n) ^{177}Lu and ^{176}Yb (d, p) ^{177}Yb→^{177}Lu reactions and (B) nuclear reactor via ^{176}Lu (n, γ) ^{177}Lu and ^{176}Yb (n, γ) ^{177}Yb→^{177}Lu reactions [55].

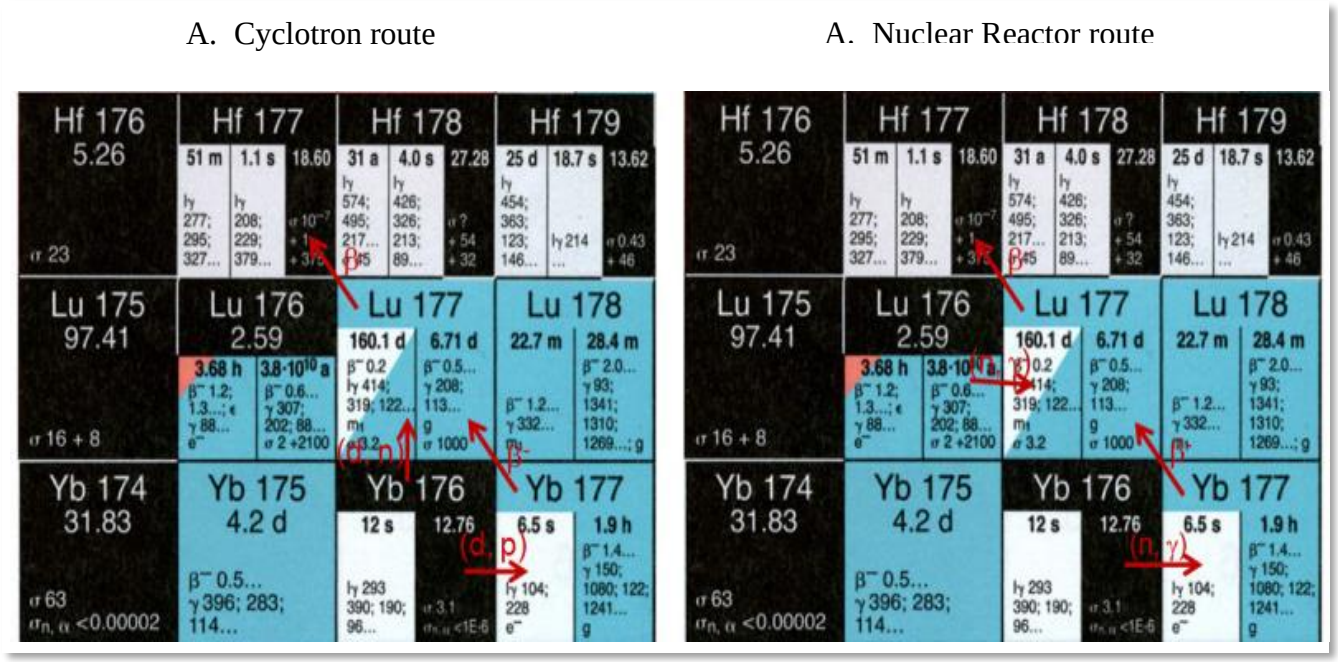


Figure 2.6 - Production of ^{177}Lu in (A) cyclotron vs (B)Nuclear Reactor

The production process necessitates deuteron bombardment of enriched ytterbium-176 targets with sufficient energy to obtain high specific activity Lu-177 leading to undesirable contaminant lutetium-177m being beyond detection limits. The deuteron induced nuclear reactions to produce n.c.a ^{177}Lu radioisotopes by using the stacked-foil activation method were studied by various researchers at slightly different parameters and reported the and reported the excitation functions which is described as the relationship between the energy of an electron and its ability to excite an atom to a particular excited state [56].

Hermanne et al. [57] performed their experiments with two stacks of high purity natural Yb foils that were 30μm thick were irradiated at energies of 21 and 15 MeV respectively, Manenti et al., Khandaker et al., and Kambali [58]–[60] shared their experience by irradiating of four to five Yb targets of different thickness, inserted between the Aluminum foils, at different incident energies and times. The excitation functions of the reactions direct and indirect reactions including measurements of ^{169}Lu, ^{174m}Lu

and ^{176m}Lu using different natural Yb foil thickness and as well as different irradiation energies.

Nuclear reactions:

^{176}Yb (d, n) ^{177}Lu (direct route)

^{176}Yb (d, p) ^{177}Yb→^{177}Lu (indirect route)

Excitation function reactions studied:

^{natural}Yb (d, n)^{169,170,171,172,173,174g,174m,176m,177g}Lu

^{natural}Yb (d, p)^{169,175,177}Yb

Upon analysis excitation functions, Manenti et. al [58] reported 177^{m}Lu was not formed neither in the case of indirect reaction nor in cases of direct reaction, that it was possible to calculate that the ratio between the activity at EOB of ^{177mLu} and ^{177g}Lu which was smaller than 0.0045% at irradiation time of 2hrs.

Kambali [60] measured the EOB yields for the direct route production and it was 0.519 MBq/µA h, and 181.1 MBq/µAh for indirect route reaction by using simulation method using the TALYS code, which is a nuclear reaction computer program which simulates basically all types of nuclear reactions. In this simulation process, deuteron was the main particle used in the calculations and simulations while the target of interest would be enriched ^{176}Yb. The range and stopping power (energy loss) of deuteron in ^{176}Yb target was simulated using the Stopping and Range of Ion in Matter (SRIM) code version 2013 and the calculated EOB yield, where Indirection production shows greater significant results that the direction production of Lu177 with corresponding deuteron energy [60].

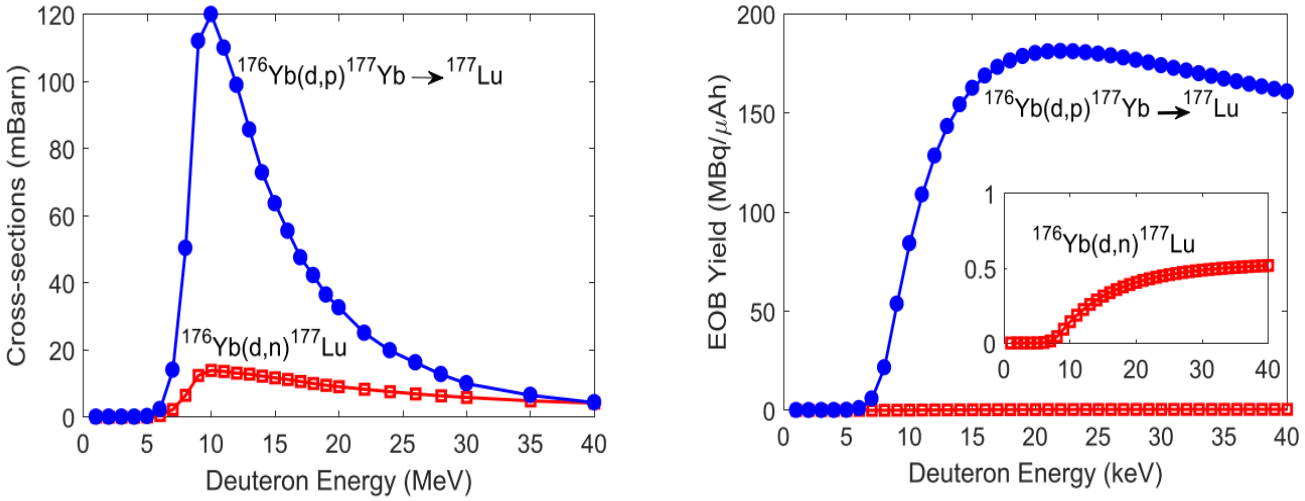


Figure 2.7. (Left): Comparison of TALYS-calculated nuclear cross-sections for ^{176}Yb(d,n)^{177}Lu and ^{176}Yb(d,p) ^{177}Yb → ^{177}Lu nuclear reactions. (Right): Calculated EOB yields of ^{176}Yb(d,n)^{177}Lu and ^{176}Yb(d,p) ^{177}Yb→^{177}Lu nuclear reactions [60].

Overall conclusions emphasized was that the best all methods of productions have advantages and disadvantages and thus in order to enhance the overall yield of ^{177}Lu and minimize the radionuclidic impurities due to extraneous Lu radioisotopes, highly enriched ^{176}Yb target must be used. Furthermore, the authors [58]–[60] emphasized that production of Lu-177 via cyclotron route by the indirect route reaction has the potential to minimize ^{177m}Lu impurity which has a half-life of 160.5 days.

1.12. Radiochemical Separation methods of Lu-177

The lutetium obtained by the indirect method must be modified from the irradiation ytterbium target. The quality of the ^{177}Lu preparation achieved is highly impacted by the separation procedure used. Separation methods of Lu-177 upon irradiation of highly

enriched Yb or Lu targets is often characterized by physical and chemical properties of elements [61] and choice of separation methods such as cementation, chromatography - ion exchange, solvent extraction, cation exchange chromatography, vacuum filtration etc. Different separation methods for separating Lu from Yb have been successful researched and different authors reports that these separating neighboring lanthanides is challenging because of their chemical similarity [50], [62]–[65].

Table 2.2 – The Physical and Chemical properties of ytterbium and lutetium

	Yb	Lu
Electronic configuration	[Xe]4f ^{14} 6s^2	[Xe]4f ^{14}5d^{1}6s^2
Ionic radius Ln^{3+} (pm)	86.8	86.1
Ionic radius Ln^{2+} (pm)	114	-
E_o $Ln^{3+/}$Ln (V)	-2.267	2.255
E_o $Ln^{3+/}Ln^{2+}$ (V)	1.05	-
Solubility in Hg	High	Low

The heaviest lanthanide is lutetium, while the lightest is ytterbium. Because they are nearby trivalent lanthanides, their chemical characteristics are quite similar, the mass ratio Yb/Lu in the irradiation target can be as high as several thousands, making Lu-Yb separation a difficult procedure. The fundamental differences between Yb and Lu are the existence of a reasonably stable oxidation state +2 for Yb as well as the high solubility of metallic Yb in mercury [6]. Unlike lutetium, the oxidation state 2+ of ytterbium is extremely stable due to the full-filed 4f subshell [6], [61].

The main reason greatly complicating the separation is, however, the presence of ytterbium in macro quantities (tens of milligram), while lutetium is found in the target only at microgram levels. Depending on the irradiation conditions and target material characteristics, the mass ratio of ytterbium to lutetium can be in the range of several hundreds to several thousands.

With regard to the intended lutetium application the requirements on the separation are quite strict:

- Reduction of the amount of ytterbium down to < 100 ng, implying decontamination factors from ytterbium higher than 10^6
- Very high chemical (< 500 µg of metals like Ca, Cu, Zn, Al, Fe, Pb per 1 Ci of 177Lu) and radionuclidic purity (< 0.1% 175Yb) of the lutetium fraction.
- High recovery of lutetium (ideally > 85%).

In this research, cementation as well as electrochemical (electro-amalgamation) separation process are extensively discussed, and further, purification processes of obtaining n.c.a Lu-177.

1.12.1. Cementation process

The cementation procedure entails subjecting the target to a suitable acid, most often HCl solution. Following this, the n.c.a $^{177}LuCl_3$ is purified, and the Yb-target is recovered. Contact electrochemical displacement of alkali metal amalgams and acetate, citrate, and other rare earth metal compounds is used in cementation to achieve practical and successful results. The cementation procedure usually includes two processes for separating lutetium from ytterbium: first, cementing an ytterbium acetate–chloride solution to sodium amalgam Na (Hg), and then electrolysis of the ytterbium solution in a separate electrolytic cell.

In cementing an ytterbium acetate–chloride solution to sodium amalgam, the Na (Hg) was prepared with electrodes 5 ml mercury and 10 cm2 Pt-foil at the cathode and anode as (12 V) respectively. Water and ethanol were used to wash the Na (Hg) recovered. The sodium content of the amalgam was tested by dissolving 500 mg of amalgam in 5 mL of 0.1M HCl, followed by titration of the remaining HCl with 0.1M NaOH. The following

equation was used to compute the molar concentration of Na in amalgam where: m – mass of amalgam V – volume of NaOH solution used in titration, d – density of amalgam ~13.2 g cm^{-3} [49].

$$C_{NA} = \frac{(0.05 - V \times 0.1)d}{m}$$

Marsh. J et.al [66]–[69] documented the separation of distinct lanthanides with sodium amalgam in the 1942, 1943 years, and as science advances, scientists are now be able to further investigate and refine these separation procedures. Upon irradiation of natural Yb_2O_3(99.999%) at neutron flux of 3×10^{14} n. cm^{-2}. s^{-1} for 6 hr. Bilewicz et al. The dependence of YbSO4 precipitation on H_2SO_4 concentration has been studied to achieve the target procedure.

To get 177Lu radiotracer, Lu_2O_3 targets were also treated under the same circumstances. Sample of 57 mg Yb_2O_3 was poured in 6 mL H_2SO_4, following that ^{177}Lu tracer was dissolved into the solution. Next, the 5M of sodium amalgam was then gradually added to the solution. After 5 minutes, when a green precipitate of $YbSO_4$ was formed, the mercury was separated. According to the reaction, in these conditions most of Lu3+ remains in solution [49].

$$Yb^{3+} + Na(Hg) + SO^{-2}_4 \rightarrow YbSO_4 + Na^+$$

Next the solution was immediately filtered through a paper filter, and the green precipitate was separated. According to Bilewicz et.al, the dependence of $YbSO_4$ precipitation on H_2SO_4 concentration resulted that 2–5M H_2SO_4 is ideal for successful Yb separation. Following the precipitation and separation of YbSO4, about 1 mg of Yb remained in the solution and the overall ^{177}Lu recovery is 73% because ^{177}Lu co-precipitated with $YbSO_4$ in a modest proportion leading to about 25% of the total ^{177}Lu being co-precipitated with

$YbSO_4$ during the procedure. The separation process was performed in the apparatus presented in Fig. 2.8 [49].

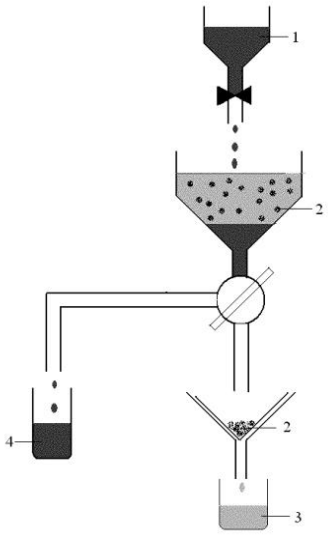


Figure 2.8. Cementation Process apparatus showing installation for YbSO4 separation. 1 – sodium amalgam, 2 – precipitated YbSO4, 3 – 177Lu solution, 4 – mercury.

In another report by Barkhausen [70], cementation process was optimized for the separation of n.c.a.177Lu from 200 mg ytterbium target based on the selective reductive separation of ytterbium with sodium amalgam followed by cation-exchange purification. The reduction is described by the following reaction:

$$Yb^{3+} + Na \rightleftharpoons Yb^{2+} + Na^{+}$$

Hydrochloric acid is used to process the irradiation Yb_2O_3, next, sodium acetate was introduced into the solution, then with addition of sodium amalgam for 90 seconds.by this process, lutetium can be obtained with a separation yield of 75% with decontamination factor from Yb of 10^6. However, special attention has to be paid to the removal of mercury compounds which are introduced into the lutetium fraction during the mixing with amalgam

In other research explored by Lebedev et al, the cementation methods applied to process for separate of n.c.a. ^{177}Lu involved a target Yb_2O_3 with mass of 200 mg dissolved in 1.4 ml 4 M HCl. Then, to a total amount of 6 ml of pH ≈ 3.4, 3 ml 4.5 M CH_3COONa and H_2O were added. This mixture was poured into a specially designed mixing vessel. Then 4 mL of Na (Hg) amalgam (0.4 percent Na) was poured., and for 90 seconds, the solution was stirred. The amalgam is removed from the system. In order to preserve the pH at 3.4, 0.2 ml 8 M CH3COOH was introduced before to the next cementation. Each of the subsequent cementation cycles is extended by 30 seconds. After four cementation cycles, almost 99 percent of the ytterbium was removed from the aqueous solution. By precipitating, the n.c.a ^{177}Lu was separated from this solution and processed as the hydroxide using 4 M NaOH. he n.c.a 177Lu was precipitated from this solution and treated as a hydroxide using 4 M NaOH. The hydroxide was then centrifuged and diluted in 2.5 mL of 0.1 M HCl. After adding 2.5 mL of 4.5 M CH3COONa to a new vessel, four further cementations with 3 mL of Na (Hg) each are done. The quantity of Yb (III) in the solution is decreased to around 0.01–0.02 percent of the starting mass after this treatment. while around 85–5 % of the n.c.a ^{177}Lu remains in the solution [71].

In the formation of ytterbium amalgam, ytterbium is reduced to a bivalent state and then to a metal. The rate of cementation by sodium amalgam is increased by adding chloride ions in the form of their sodium or potassium salts to the solution. It has been well known that the cementation of aqueous ytterbium solutions on sodium amalgam occurs quickly when the pH of the working solution rises from 3 to 6 and above, based on the duration of contact with the amalgam, the starting pH, and the stirring technique.

1.12.2. Electrochemical (electro-amalgamation) separation process

This is the process that entails the selective reduction of Yb^{3+} to Yb^{2+} [6] and preferred transfer onto a mercury cathode, which takes use of Yb2capacity +'s to create amalgams with Hg. This technique is appealing for the following reasons: An analysis of the redox potentials of Yb and Lu suggests that Yb may form the bivalent state, but a stable bivalent state for Lu is unknown. While Yb2+ is known to amalgamate, Lu3+ is not. As a result, aqueous electrolytes make it difficult to deposit Lu on the Hg cathode. Because of its high hydrogen over-voltage, this method allows for electrolytic reduction of Yb3+ to Yb2+ in a moderately acidic solution. This property ensures that Yb2 is not reoxidized. [72].

A mercury-pool cathode electrochemical route invented by Chakravarty et al. [73] is considered on two-cycle electrolysis in lithium citrate medium. The electrolytic reduction of Yb^{3+} in acidic pH could be described by the following reactions:

$$Yb^{3+} + e^{-} \rightarrow Yb^{2+}$$

$$Yb^{2+} + 2e^{-} \rightarrow Yb^{0}$$

The overall potential for this reaction is E0= - 2.27 V

In a lithium citrate medium, ^{177}Lu was separated from a $^{177}Lu/Yb$ solution using a two-cycle electrolysis technique. For the quantitative deposition of Yb in the presence of 177Lu, the initial electrolysis was carried out for 50 minutes at pH 6 in the 177Lu/Yb feed solution with a voltage of 8 V with a platinum electrode as anode and mercury as cathode. Fresh electrodes were used for the second electrolysis, which was done under the same circumstances as the first. Gamma ray spectrometry and atomic absorption spectrometry were used to assess the radionuclidic and chemical purity of ^{177}Lu [73].

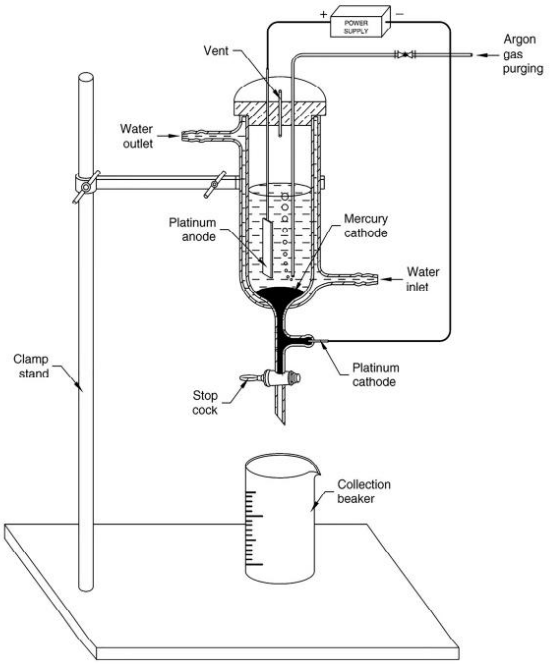


Figure 2.9: Illustration of ELM process

In another process of ELM separation method, the irradiated target was mixed into 1mL 0.05N HNO3. This solution includes ^{175}Yb, ^{169}Yb and ^{177}Lu was mixed with 15mL lithium citrate (0.15M) as an electrolyte. By using a constant potential of 10V and adjusting the pH of electrolyte to 6-7 for 45 minutes, electrolysis was done. The final production yield ELM procedure was 88.83%, the production process is shown in figure [74].

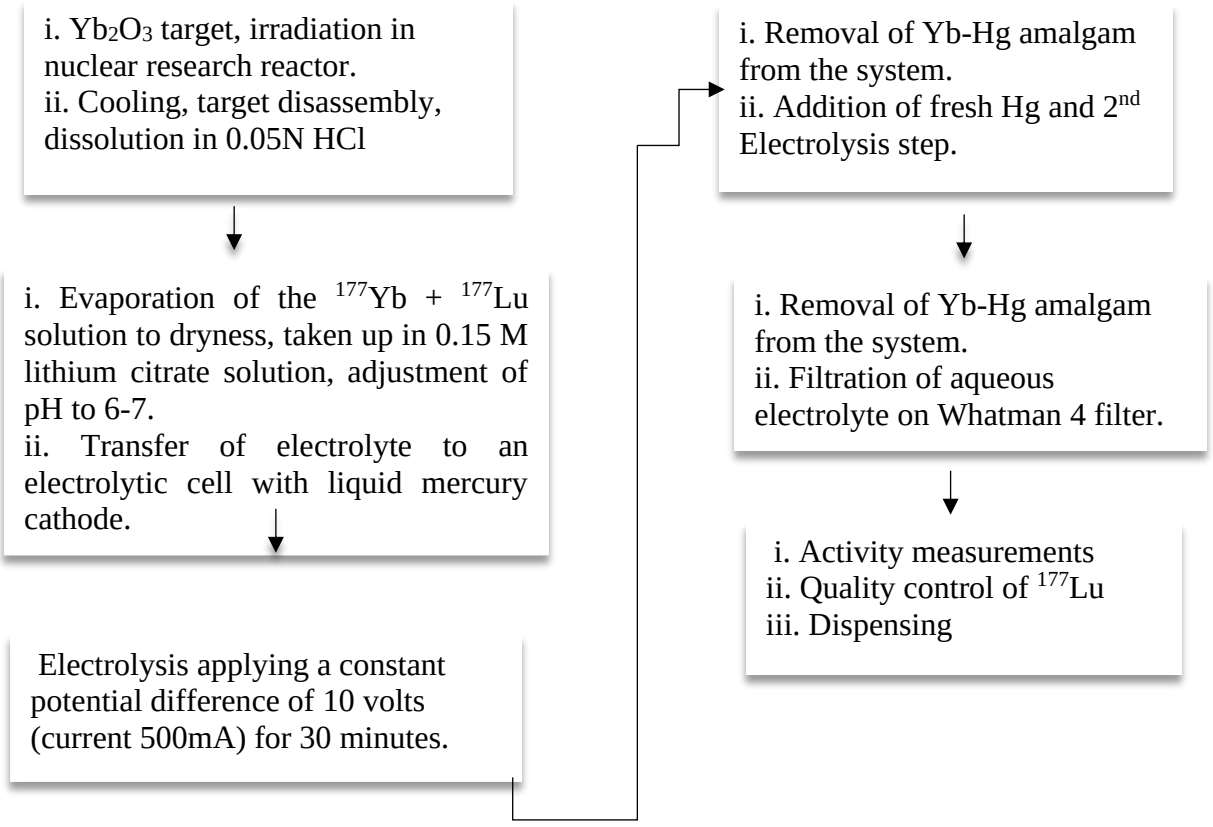


Figure 2.10. Electro-amalgamation process

In a similar technique, P. P. Boldyrev et al. conducted cementation studies utilizing ytterbium with a natural isotopic composition target ^{169}Yb with a 10^6 Bq activity. The solution had a volume of 10 mL and a concentration of 1 mg/mL of ytterbium, they measured the solution flow rate of 5.5 mL/min, and the amalgam content was 0.3 wt% sodium [75]. Tarasov et.al [76] Tarasov et al. conducted this this strategy using a prototype unit for electrolytic separation of ytterbium from lutetium in a "hot" cell was built. The unit's major constructive components are as follows and shown in figure:

- Quartz electrolysis cell with three platinum cathode current lead wires at the bottom. The electrolyte had a capacity of 250 mL and the mercury had a volume

of 100 mL for electrolysis. The surface area the electrolyte and mercury was 95 cm^2.

- A platinum wire helical anode is inserted in the electrolysis cell cap. Also, on cap were also mounted a tiny electromotor to stir mercury, a laboratory thermometer (or a thermocouple) to control the temperature of the electrolyte, and a sampling tube to collect electrolyte samples [76] .

By using this prototype unit, ^{177}Lu and ^{175}Yb radioactive tracers were used to investigate the optimum condition for galvanostatic extraction of ytterbium into mercury cathode. In this process, electrolytes were made up of solutions comprising 0.10–0.15 mol/L lithium citrate and 0.4 g/L ytterbium chloride. The ideal cathode current density was determined to be between 25 and 40 mA/cm2, and after 3–5 hours of electrolysis, the ytterbium isolation coefficient reached 99%.

Figure 2.11: The prototype device for electrolysis-based separation of ytterbium and lutetium on a mercury cathode [76].

1.12.3. Other methods of separating Lu-177

Extraction chromatography (EXC) separation is a separation technique that combines the selectivity of solvent extraction with the simplicity and efficiency of column chromatography [77]. Two columns, marked as column 1 and column 2, were prepared to determine the best conditions for this Lu/Yb separation. 0.1N nitric acid was used to wash 10 g of LN2 resin (25-53µm particle size) and 10g DGA resin (50-100µm particle size) for 24hrs [77].

Well-washed LN2 resin and DGA resin were used to fill columns (1) and (2), respectively. The columns were then controlled with 50 mL of distilled water, 50 mL of 0.1N HNO3 for column (1), and 0.05N HCl for column (2), followed by another 50 mL of distilled water. The irradiation target (in 0.1N HNO3) was loaded at a flow rate of 2 ml/min on the column (1), washed with 0.1N HNO3 and 1.5N HNO3, and eluted with 4N HNO3. The eluted solution was collected in a 5mL bed volume and examined using the HPGe detector for Yb and Lu radionuclides. This method resulted in an overall output of 82 percent 177Lu [77].

Satoshi Watanabe et.al. [78] conducted experiments on the methods of reversed-phase ion-pair liquid chromatography in order to separate NCA ^{177}Lu from macroscopic amounts of the Yb target, providing the labeling yield of the Lu-177-labeled antibody increased from < 5 to 88 %. Approximately 1.1 GBq of 177Lu (end of bombardment) can be produced by irradiating 2 mg of $^{176}Yb_2O_3$ for 10 days at $1.9x10^{14}ncm^{-2}s^{-1}$ with 2.85barn at the cross section of 176Yb. This quantity is sufficient for animal experiments designed to investigate the therapeutic effects of ^{177}Lu-labeled antibodies. For the production of177Lu on larger scale for human therapies, a method capable of separating more than several tens of mgof$^{176}Yb_2O_3$ is required. Therefore, a two-step separation method will be necessary in which the rough separation of ^{177}Lu from Yb, such as solvent extraction or electro-chemical

separation, is first performed, and is followed by purification using the reversed-phase ion-pair liquid chromatography technique developed in this study [78].

1.13. Purification of Lu-177

Ytterbium (Yb) is a rare-earth element and in the earth's crust, is a mixed composite oxide mineral resource. Ytterbium metal has a high vapor pressure and is hard to refine and contains large amounts of volatile elements and impurities. The purification and recovery of ytterbium in the Lu-Yb-Hg involves the method of high temperature saturated dissolution, low temperature recrystallization, high temperature reduction and vaporization-based removal of impurities. Ion exchange (IE) is a water purification technique that removes dissolved pollutants from water and other liquid solutions. This approach can also be used to purify liquids in radiochemistry labs. Ion exchangers are high-molecular-weight compounds that are insoluble in water and a variety of other solvents and capable of exchanging their own active ions for those from the surrounding electrolyte.

The TK221 Resin is composed of a diglycolamide and phosphine oxide. principal uses of TK221 Resin lies in purification and conversion of heavy lanthanides such as Lu from highly concentrated acidic solutions into dilute HCl (usually 0.05M HCl) conditions. t enables the elution of Lu, for example, in a lower volume than DGA, N Resin[79]. It is also crucial in the purification of Lu-177. Because lanthanides are often extremely well held at 3M HCl concentrations, heavy lanthanides can be eluted in dilute HCl [79], [80].

According to Lebedev et al. [50] (see section 2.4), ^{177}Lu was separated from the residual Yb (III) (30 g) using cation exchange chromatography. La/177Lu, Yb/$(OH)_3$ co-precipitate the n.c.a ^{177}Lu. The hydroxides were treated in 0.1 M HCl after centrifugation to eliminate any potential mercury complexes Hg_xCl_y. Lanthanides are absorbed from this solution on

the head of an Aminex A6 column (2.0 80 mm). After the resin has been converted to $NH^{4+,}$ ^{177}Lu was eluted with 0.07 M -HIB at pH 4.7. In the presence of 50 g Yb (III), n.c.a ^{177}Lu may efficiently separate, corresponding to the effectiveness of the cementation cycle. With Yb(III) contaminations of 0.1 percent of the original Yb(III) traces, i.e. 10 ng Yb(III) for the 10 g Yb(III) experiment, around 90% of the n.c.a ^{177}Lu may be separated for low beginning levels of 50 g Yb(III). If just the maximum of the n.c.a ^{177}Lu elution peak of roughly 80% is taken into account, the quantity of Yb (III) can be lowered to 1 ng [50], [81].

The purification of ^{177}Lu/Yb using Lewatit® MonoPlus TP 214, which is a macroporous resin with chelating thiourea groups designed for the selective removal of mercury, precious metals of the platinum group, gold and silver. It is macroporous, beige/opaque, styrene resin with mean bead size of 0.55 +/- 0.05 mm. The bead sized of Lewatit® MonoPlus TP 214 are mechanically and osmotically more stable than ion exchange beds with a heterodisperse bead size distribution. Additionally, this resin is suitable for the removal of mercury (Hg) and recovery from Yb/Lu solution. Other applications of using this resin are in the in mercury from ground water metal separation and recovery in hydrometallurgy, e.g. for gold (Au), silver (Ag) and platinum metals (Pt, Pd, Ru, Rh) as well preconcentration of palladium(ii) ions from hydrochloric acid - sodium chloride solutions [82], [83].

1.13.1. Neutron Activation Analysis

The physical phenomena upon which NAA are based are the properties of the nucleus, radioactivity, and the interaction of radiation with matter. The NAA method relies on the measurement of either these characteristic prompt or decay gamma rays for identifying elements and determining their amounts present in samples. The

concentrations of trace elements in a sample can be calculated with equations provided the reaction rates, detector efficiency curve, half-lives, and decay schemes of the radionuclides are known [31], [84].

1.14. Quality control of Radiopharmaceutical.

The (radio)/pharmaceutical component should be free of any impurities, toxicity or physiological effects. The radiopharmaceutical should not disassociate in vitro or in vivo and should be readily available or easily compounded. Impurities originates from drug substance synthetic processes in the starting materials and intermediates, reagents, ligands and catalysts, by-products of the synthesis, products of over-reaction. Radiochemical impurities arise from decomposition due to the action of solvent, change in temperature or pH, light, presence of oxidizing or reducing agents and it is important to have quality control radiopharmaceuticals. Radiopharmaceuticals must undergo strict quality control and measurements includes radiochemical purity test, chemical purity and biological tests. (Ganesh, 2018). Currently, most referenced gamma spectrum analysis by HPGe detector for radioisotope Lu-177 without impurities after separation from targets is shown in figure 12 [62].

The accumulation of 177mLu and concerns:

Radiation dose: As hospitals use their ^{177}Lu for radiopharmaceutical manufacture up to one week after EOB, the ^{177m}Lu/177Lu ratio is expected to be increased. The typical therapeutic dosage of 177Lu is between 7 and 9 GBq. When the ^{177m}Lu/^{177}Lu ratio is 0.02 percent, a dosage contains roughly 1.4–1.8 MBq 177mLu [6].

Laboratory waste: The loss of radioactivity throughout the radiolabeling procedure and treatment is generally 2–5% of the 177Lu activity, corresponding to levels of 28–90 kBq 177mLu. Because of the legal emission limit for 177mLu waste (10 Bq/g), all laboratory radioactive waste must be collected separately and delivered to a radioactive waste management facility to decay. With a half life of 160.1 days, 177mLu requires a significant amount of time to decay [6].

Waste water: After receiving 177Lu-labeled octreotide, a patient excretes roughly 80% of the supplied dosage (1.45 MBq 177mLu) through urination. The patient-excreted activity in urine and feces must be held in waste water, where 177mLu can accumulate in the radioactive waste water storage tanks. The highest allowable radioactive content of 177mLu in municipal sewage, according to European radiation safety regulations, is 50 kBq/m3. This implies that radioactive waste water from holding tanks must be heavily diluted before being discharged into the local sewage system. The presence of 177mLu in radioactive waste water holding tanks may exceed activity limitations alone or in combination with other nuclides (sum activity) and must be examined in each situation [6].

While the radiation dose to patients from ^{177m}Lu (0.01 percent –0.02 percent) is insignificant [53], the problem of safe handling and disposal of residual quantities of ^{177m}Lu by hospital users may emerge as a major roadblock, which can hardly be avoided, in principle, through the storage of radioactive wastes that is customary in hospitals. Despite the disadvantages listed above, ^{177}Lu acquired through the (n,) approach is favored by many hospitals because to the cost-effective availability of adequate quality and quantity on demand [6]. This can be seen as the window of opportunity to lay the basis for realizing the widespread radiopharmaceutical use of ^{177}Lu.

^{177}Lu metastable and its complications in radiolabeling

By the irradiation of ^{176}Lu target, an effect of producing a long-lived radionuclide ^{177m}Lu that has a half-life of 160d, which can be a disadvantage in such way that the radionuclidic purity of Lu-177 may pose have waste management problems in the hospitals [85].

Owing to the low cross-section (~7 b) of the ^{176}Lu (n, γ) ^{177m}Lu reaction the yield of ^{177m}Lu is mostly low under most irradiation conditions, furthermore, medium flux conditions the level of ^{177m}Lu in ^{177}Lu is less than 0.02% and thus may be seem as not significant issue, but ^{177m}Lu being a radionuclidic impurity, it can absorbed in the tissues where the uptake of ^{177}Lu-based radiopharmaceutical occurs and period of absorption of can be much more prolonged compared to ^{177}Lu due to longer half-life [85].

Moreover, if metabolization of the targeting agent occurs, free ^{177m}Lu can be excreted or skeletal uptake may occur. In other aspect waste management of impurities tend problematic and hence in each countries waste disposal protocols have to be adhered to [86]. For instance, if small amount of μCi of ^{177m}Lu would be present in a curie of ^{177}Lu used in a nuclear medicine clinic, the containment and post-decay release of the radioactive waste generated has to be carefully managed by design of appropriate delay tanks [87]. The Figure 2.12 (a) shows gamma spectrometry without impurity detected figure 2.12 (b) with ^{177m}Lu impurity detected if the end product of Lu has the long-lived impurity

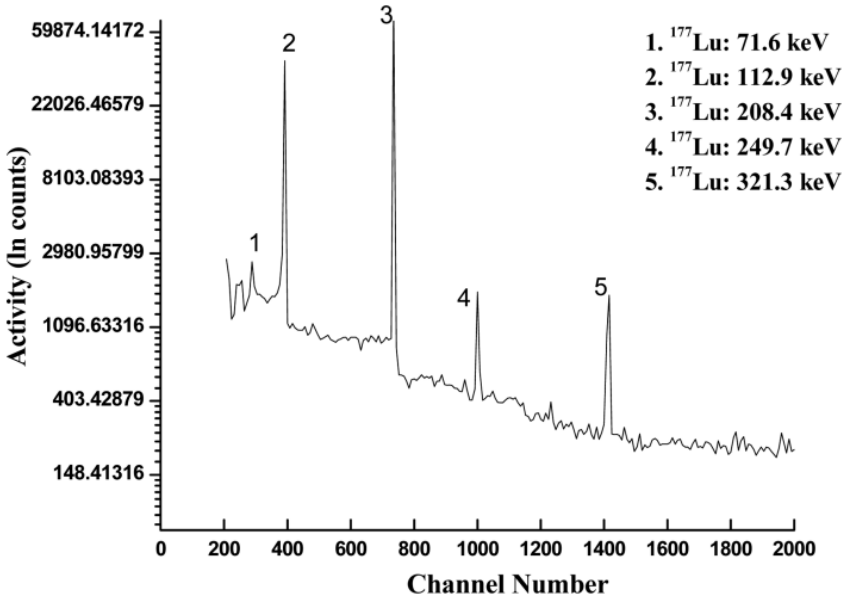
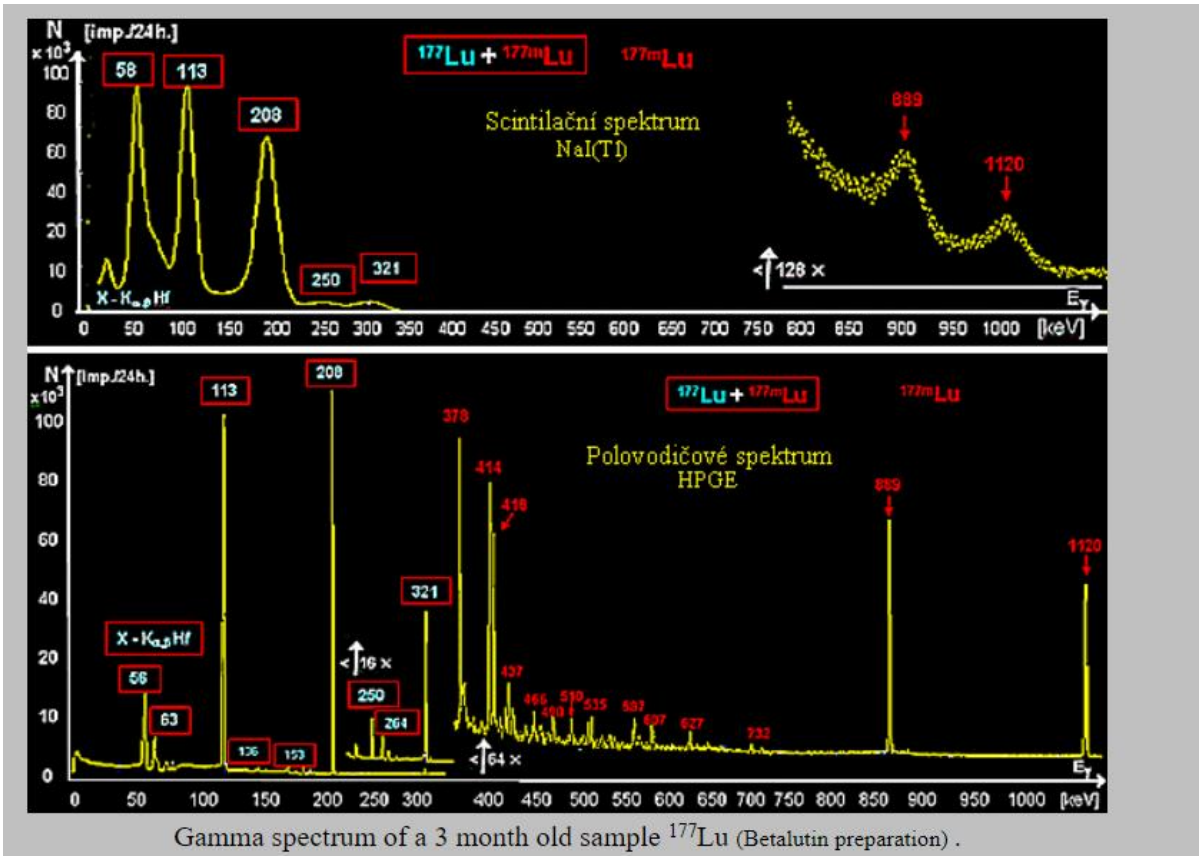


Figure 2.12 a. Gamma spectrum of Lu-177 [62]



Gamma spectrum of a 3 month old sample ^{177}Lu (Betalutin preparation) .

2.12b Gamma spec with 177mLu impurity detected [6], [34], [35].

1.15. Protocol of Lu-177-DOTATATE radiolabeling and Biodistribution control

Upon Lu-177 production whereby target material Lu_2O_3 (99.99%) is accurately weighed by analytical balance, this target is contained in quarts ampoule, then placed in aluminum containers that are used for irradiation. Duong Van Dong et. al [88], Samina Roohi et.al.[89] reported production and radiochemical processing of ^{177}Lu in the form of $^{177}LuCl_3$ salt by the method wherein:

- Typically, 100mg of iso-topically enriched Lu_2O_3target (52% in ^{176}Lu) was dissolved in concentrated HCl to get $LuCl_3$.
- The resulting solution was then dried in a quartz tube in desiccators and reconstituted with ultrapure water - dried it again, sealed the tube in aluminum sheet for irradiation.
- The sample was irradiated at a thermal neutron flux of $1.5x10^{14}n.cm^{-2}s^{-1}$ for 18 hr.
- The irradiated target was allowed to cool for 12 hr and dissolved in gently warm HCl solution (pH 3-4) followed by cooling to room temperature and filtering through 0.22mm Millipore filter paper to obtain pure $^{177}LuCl_3$. Thus, obtained $^{177}LuCl_3$ could be used for therapeutic dose of 177Lu-DOTATATE [88], [89].

Combining the radionuclide ^{177}Lu with the somatostatin analogue DOTA-TATE, [^{177}Lu] Lu-DOTA-TATE delivers ionizing radiation specifically and selectively to tumor cells expressing SSTRs [38]. Radiolabeling and mechanism is shown in figure 13 and it is vital to note that [^{177}Lu] Lu-DOTA-TATE should be produced in a GMP (Good Manufacturing Practice)-compliant automated radiosynthesis by reacting n.c.a. (no-carrier added) [^{177}Lu] $LuCl_3$ with DOTA-TATE under suitable condition[38].

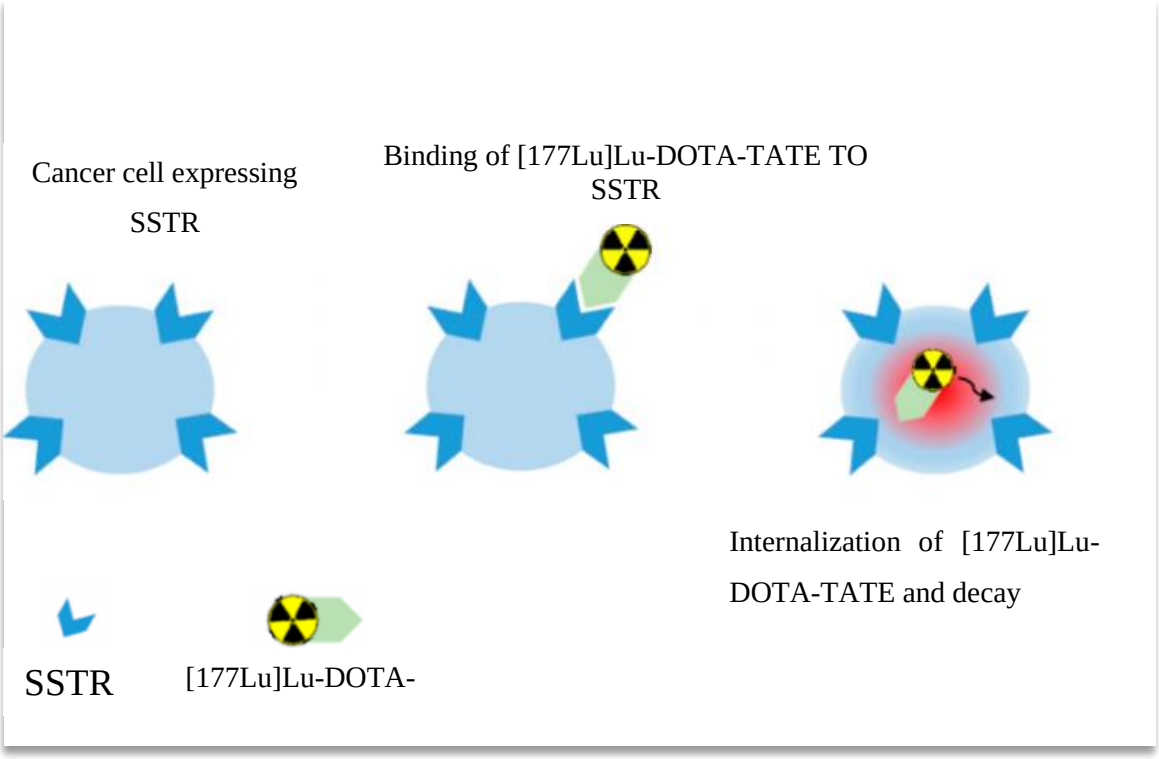


Figure 2.13 - Radiolabeling mechanism of [^{177}Lu] Lu-DOTA-TATE

The labeling of DOTATATE kit with ^{177}Lu involves the freeze-dried cold kit of DOATATAE reconstituted with sterile water and diluted to a pH of 5 followed by the addition of $^{177}LuCl_3$ solution with increasing DOTATATE concentration such as 1,2,3,4, or 5 times as compared to ^{177}Lu. Following the preparation of ^{177}Lu-DOTATATE and cooling at room temperature, the radiochemical mixture was subjected for quality control analysis using chromatography process [89]. According to Duong Van Dong et. al [88], radiolabeling with DOTATATE was carried out by the demonstrations in figure 2.14.

The characterization of the labelled conjugate and the complexation yield were determined by paper chromatography in 50% aqueous acetonitrile. The radiochemical purity of the labelled product was estimated by PC, TLC and HPLC analysis using the gradient elution technique described above. After preparation of ^{177}LU – DOTATATE, Optimization studies of ^{177}Lu labelling of DOTATATE various parameters such as ligand

concentration, incubation time and temperature, stability, quality control, labeling efficiency, measuring can be carried out[88].

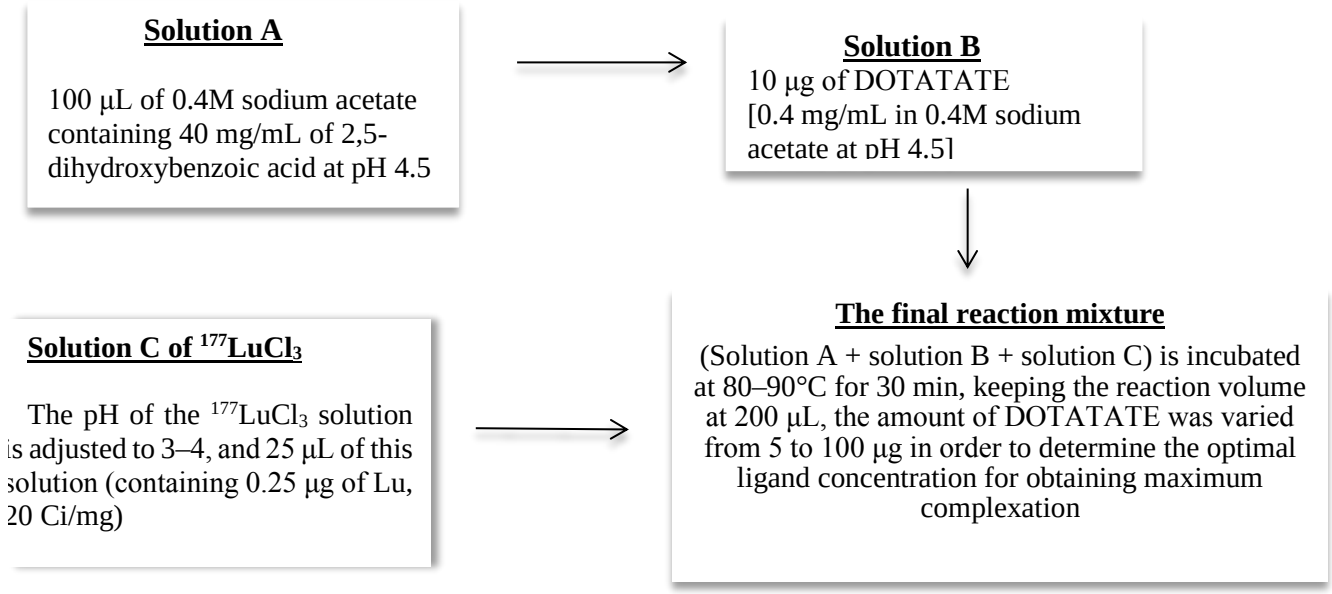


Figure 2.14. Protocol of Lu-177-DOTATATE radiolabeling and Biodistribution control

Biodistribution of Lu-177

Biodistribution is fundamental to identifying target organs and anticipating safety and efficacy, tracking where compounds of interest travel in an experimental animal, and Duong Van Dong et. al and Roohi et.al [88], [89]. studied the biodistribution pattern of ^{177}Lu labeled FDK of DOTATATE in normal rats each weighing 40-50 g in a group of 3-5 where the ^{177}Lu-DOTATATE solution prepared above was further diluted with saline to 25 MBq activity/mL. An aliquot of 200mL of ^{177}Lu-DOTATATE solution was then administered in animals through the tail vein of rats. In both reports, reported radiochemical purity is more than 99%, in vivo biodistribution studies in normal mice revealed that the ^{177}Lu-DOTATATE have suitable pharmacokinetic properties [88], [89].

In summary, understanding the radiochemical properties of Lu-177 helps researchers improve methods to treat cancer and other related diseases, the more studies performed,

the more research that is done, the more likely it is to improve on finding the treatment for the cancer.

Chapter 6: Financial Management

Introduction

This section outlines the comprehensive description and analysis of the financial and economic aspects of the work performed when producing radioisotope Lu-177. In this work, the indirect route for production N.C.A. ^{177}Lu by irradiating the natural Yb_2O_3 >99.99% and enriched Lu_2O_3 target material at neutron flux of 2.0 x 10^{13} $n.cm^{-2}.$ s^{-1} for 30 minutes at Nuclear Research Reactor IRT-T for application in nuclear medicine was carried out. The main objective in this study was to apply radiochemical separation methods based on cementation processes for separating Lutetium from Ytterbium targets, followed by purification using cation exchange chromatography with Lewatit MonoPlus T214 resin. Radiochemical measurements were carried out using HPGe detector and trace amounts of Hg and Yb were detected, further to achieve a radioisotope with no impurities, purification process was applied and radiochemical assessment by the neutron activation analysis which resulted in a pure product with no mercury and small amount of Yb that is negligible. The produced radioisotope N.C.A ^{177}Lu is suitable to application in nuclear medicine, treatment and diagnosis of cancer education, radiobiology (biodistribution pattern of ^{177}Lu in rats), Research in modelling experiments and clinical measurements.

6.1. Financial management, resource efficiency and resource saving

Financial management is the effective handling of money through planning, organizing, directing and controlling funds in any corporation or company with the aim of solving planning and preparation of research work, budget calculation for research work and development of evaluation of commercial potential. The purpose of this section discusses the issues of competitiveness, resource efficiency and resource saving, as well as financial costs regarding the object of study of this Masters' thesis. Competitiveness analysis is carried out

for this purpose. SWOT analysis helps to identify strengths, weaknesses, opportunities and threats associated with the project, and give an idea of working with them in each particular case. The development of the project requires funds that go to the salaries of project participants and the necessary equipment, a complete list is given in the relevant section. The calculation of the resource efficiency indicator helps to make a final assessment of the technical decision on individual criteria and in general

6.2. Pre-research analysis

The research perspective of production of Lu-177 by indirect irradiation of Yb_2O_3 and Lu_2O_3 targets is sought to establish the end product medical radioisotope n.c.a $^{177}LuCl_3$ for modeling experiments. Upon irradiation, Yb_2O_3 and Lu_2O_3 targets are processed into radioactive tracers Yb_2Cl_3 and Lu_2CL_3 respectively, after this; n.c.a $^{177}LuCl_3$ was produced by indirect route method using the non-radioactive Yb_2O_3 solution activated with radioactive tracers and Hg. Next, Yb and Lu must undergo separation process by cementation methods then purification process by cation exchange chromatography using Lewatit MonoPlus T214 resin to further purify Yb from mercury and recover Yb for new production. Radiochemical analysis was then performed using HPGe detector and Neutron Activation Analysis methods. This research is meant for researchers in hospital clinical measurements and modelling experiments nuclear medicine departments, researchers in high institution of learning for and education for studying biodistribution of ^{177}Lu (in rats) to improve the best optimal production routes of ^{177}Lu. Assessment of the commercial value of the development is dependent the production process depends on production route, separation methods, purification process, separation factor, achieving the highest specific activity and purity of the radioisotope as different radiopharmaceutical companies and nuclear research reactors are performing same investigation and preferably by direct route production and the drawbacks of the direct procedure involves long-lived Lu-177m (160d) which is an unwanted impurity, in conclusion,

the indirect route a method chosen in this research provides a medical radioisotope with no long-lived Lu-177m (160d).

Potential consumers of the research results: Target market and segmentation

To study consumers of research results, it is necessary to segment the market. The target market that would be interested in the outcomes of student's investigation research results of producing of Lu-177 includes university institutions for nuclear medicine, radiobiology, oncology research departments for studying the biodistribution of Lu-177; hospital would use the results for treatment of cancer clinical trials and radiopharmaceutical companies for which is also segmented into diagnostic and therapeutic by application of Lu-177 in oncology, cardiology, neuroendocrinology, nephrology, musculoskeletal, respiratory and others, hospital would use the results for treatment of cancer, clinical trials.

6.3. Competitiveness analysis of technical solutions

In order to find sources of financing for the project, it is necessary, first, to determine the commercial value of the work. Analysis of competitive technical solutions in terms of resource efficiency and resource saving allows us to evaluate the comparative effectiveness of scientific development. It is important to analyze possible technical solutions and choose the best one based on the considered technical and economic criteria. Evaluation map analysis and criteria for ^{177}Lu-produced at the nuclear research reactor IRT-T by irradiating Ytterbium (Yb) and Lutetium Lu targets in the form of Yb_2O_3 and Lu_2O_3 is characterized by:

- Equipment and materials: availability of resource to produce Lu-177, reagents, materials and Equipments.
- Determination of theoretical yield of Lu-177: a measure of the amount of Lu-177 can be produced under same conditions (natural origin of target, same neutron flux density, mass of target and time of irradiation);

- Separation Process: ease of separation methods of Lu from Yb targets and purification process of Yb from mercury tracer.
- Degree of Impurities: measure of impurity via neutron activation analysis by acquiring gamma spectrometry after separation and purification using HPGe detector (GX1018 Canberra).
- Determination of radionuclidic purity - purity of obtained Lu-177
- Safety: measure of safety throughout the production/work process
- Development cost: Project cost
- Development prospects the ability of the project to develop successfully in the future in the required area.

The criteria were evaluated using position of the research and competitors and evaluated for each indicator on a five-point scale, where 1 is the weakest position and 5 is the strongest. Analysis of competitive technical solutions is determined by the formula:

$$C = \sum P_i \cdot W_i$$

Where C - the competitiveness of research or a competitor; W_i– criterion weight;

P_i – point of i-th criteria.

In this research study, Cementation process – Pi1 , Electrochemical method – Pi2,

Table 1 - Evaluation card for comparison of competitive technical solution

Evaluation criteria	Criterion Weight	Points		Competitiveness	
		P_{i1}	P_{i2}	C_{i1}	C_{i2}
1	2	3	4	5	6
Technical criteria for evaluating resource efficiency					
1. Demand for materials and equipment	0,05	3	4	0,6	0,8
2. Yield of Lu-177	0,19	4	3	0,12	0,18

3. Ease of separation and purification	0,06	5	3	0,24	0,24
4. Degree of Impurities	0.04	3	4	0.16	0.15
5. Safety	0,06	4	3	0,24	0,18
6. Radionuclide purity	0,2	5	2	1	0,4
Economic criteria for performance evaluation					
1. Development cost	0,2	2	4	0,4	0,8
2. Development prospects	0,2	4	2	0,8	0,4
Total	1	30	25	3,56	3,15

P_{i1} and P_{i2} are the electrochemical and cementation method respectively used in the separation of Lu 177 from impurities. C_{i1} and C_{i2} are the competitors in the radio pharmaceutical industries using direct separation methods where the end product has impurities of Lu177m. In summary, produce n.c.a Lu-177, the indirect route was chosen by irradiating highly enriched Yb and Lu target is very expensive, and cementation process as a method of separation Lu from macro-element of Yb is relatives faster and has mercury as the impurity at the end of the production process, however; with following purification process by cation exchange resin using Lewatit MonoPlus T214 resin, the it is possible to obtained a radioisotope with no mercury.

6.4. SWOT Analysis

Complex analysis solution with the greatest competitiveness is carried out with the method of the SWOT analysis: Strengths, Weaknesses, Opportunities and Threats. The analysis has several stages.

The first stage consists of describing the strengths and weaknesses of the project, identifying opportunities and threats to the project that have emerged or may appear in its external environment.

Strengths: These are the factors that characterize the competitive side of a research project. Strengths indicate that a project has a distinctive advantage or special resources that are special in terms of competition. In other words, strengths are the resources or capabilities available to the project management that can be effectively used to achieve the goals set. At the same time, it is important to consider the strengths both from the point of view of the project management and from the point of view of those who are still involved in it.

Weaknesses: This describes a flaw, omission, or limitation of a research project that hinders the achievement of its goals. This is something that does not work well within the project or where it has insufficient capabilities or resources compared to competitors.

Opportunities: These are any preferred situation in the present or future that occurs in the project environment, such as a trend, change, or perceived need that supports the demand for a result that allows the project management to improve their competitive position.

Threat: This is any undesirable situation, trend or change in the environmental conditions of a project that is destructive or threatening to its competitiveness in the present or future. The threat may be a barrier, restriction, or anything else that may cause problems, destruction, harm, or damage to the project.

The SWOT analysis of the research is described in Table 2.

Table 2 - SWOT analysis

	Strengths: S1. Declared efficiency and energy efficiency of technology. S2. Environmental friendliness of the technology. S3. Lower production cost	Weaknesses: W1: Limited time to collaborate with theragnostic and radiobiology department to research more about biodistribution of Lu-177 in rats. W2. Lack of some of necessary equipment for electro-amalgamation. W3: Duration of data analysis was very long

	compared to other technologies. S4. Availability of budget funding. S5. Qualified stuff.	W4: Attending conferences in medium language of instruction.
Opportunities: O1. Use of the innovative TPU Nuclear research reactor IRT-T. O2: Data analysis for Neutron Activation Analysis using equipment HPGe (GX1018 Canberra). O3: Optimization of separation and purification process to recycle Yb from Hg tracer. O4: Promising technology production of Lu-177 O5. Emerging use of medical radionuclide Lu-177 in nuclear medicine.	The possibility of using the measurement results in further research in various fields of science (nuclear medicine and theragnostic departments)	Training of nuclear medicine technologists, radiation biologist, medical physicist to work with radiopharmaceuticals in hospitals. Carrying out biodistribution of Lu-177 in local radiobiology laboratories will help increase the interest in research and speed the process of clinical trials.
Threats: T1: Radioactive substance. All the reagents and radioactive substance are handled by qualified stuff T2: Separation technique of using cementation process, which introduces mercury which may occur in impurity. T3: Developed competition of production technologies. T4. Restrictions on the export of technology.	Improving the quality of separation methods will increase competitiveness in the market.	Training with nuclear engineers to produce medical radioisotopes

In conclusion, the challenges are not difficult to solve, and in the near future they can easily be solved with increasing experience through research.

SWOT matrix

It is needed to identify the strengths and weaknesses of the research project to the external environmental conditions to determine the need for strategic changes. For this it is necessary

to build the project matrices to helps to understand the various combinations of relationships between the areas of the SWOT matrix. It is possible to use this matrix as one of the bases for evaluating strategic choices. Each factor is marked "+" (meaning a strong match of strengths to capabilities), " - " (meaning a weak match).

Table 3 - Strengths and Opportunities Project Matrix.

	S1	S2	S3	S4	S5
O1	+	+	+	+	+
O2	+	+	+	-	+
O3	+	-	+	-	+
O4	+	-	-	+	-
O5	-	-	-	-	+

Analysis of this interactive spreadsheet showed correlated strengths and opportunities: O1S1S3S4S5, O2S1S2S4, O3S1S3S4, O5S5.

Table 4 - Weaknesses and Opportunities Project Matrix

	W1	W2	W3	W4
O1	-	-	-	-
O2	-	+	-	-
O3	-	-	-	+
O4	-	-	-	+
O5	+	-	-	+

The correlations of weaknesses and opportunities are as follows: O1W5, O2W2, O3W4, O4W4, O5W1W4. The next step in project analysis is to identify the correlation of strengths and threats.

Table 5 - Strengths and Threats Project Matrix

	S1	S2	S3	S4	S5
T1	-	-	+	-	+
T2	+	+	+	-	+
T3	+	-	+	+	-
T4	-	-	-	-	-

The correlations of threats and strengths are as follows: T1S3S5, T2S1S2S3S5, T3S1S3S4. The next step in project analysis is to identify the correlation of weaknesses and threats.

Table 6 - Strengths and Threats Project Matrix

	W1	W2	W3	W4	
T1	-	-	-	-	T1
T2	-	+	+	-	T2
T3	-	-	+	-	T3
T4	-	-	-	-	T4

The correlations of threats and strengths are as follows: T2W2W3, T3W3.

Based on the results of the analysis of this matrix, it can be concluded that

the difficulties and challenges that this research project may face are offset by the existing strengths of the research.

6.5. Project Initiation

This section describes the initial goals and content and fix initial financial resources. The internal and external stakeholders of the project are determined, which will interact and influence the overall result of the scientific project. Information about the stakeholders of the project, the hierarchy of project goals and criteria for achieving goals is presented in the table below.

6.5.1. The goals and results of the project

This section describes stakeholders of the project in table 7. The Project stakeholders are persons or organizations that are actively involved in the project or whose interests may be affected both positively and negatively during the execution or as a result of the completion of the project.

Table 7 – Stakeholders of the project

Project stakeholders	Stakeholders of the project expectations
Medical centers and pharmaceutical companies, nuclear and scientific centers.	Convenient in usage for low-cost and efficient technology for the production of Lu-177; High chemical purity and isotope extraction yield High radioisotope purity
TPU nuclear reactor IRT-T and other nuclear research Institutions producing radioisotopes, and Radiopharmaceutical	To produce radioisotopes with high specific activity using direct and indirect route for nuclear medicine applications. Use the produced yield of ^{177}Lu for preparations of biodistribution studies and radiopharmaceuticals.
Patients with cancer	The acquired results could be a ground breaking finding for research in TPU and starting clinical trial with Lu-177.
South African government companies that produce radioisotopes	To use knowledge and experience gained to put in the resources of South Africa, producing the isotope of interest for nuclear medicine, oncology and theragnostic research.

Information about the hierarchy of project goals and criteria for achieving goals is given in the table below.

Table 8 – Project goals and results

Project goals	Production of n.c.a Lu-177 at the IRT-T research reactor for application in nuclear medicine.
Expected results of the project	Separation of Lu-177 from a Yb target, determination of impurities of the resulting Lu-177.
Acceptance criteria of the project result	Satisfactory radionuclide purity and degree of Lu-177 separation from the Yb_2O_3 target
Requirements to the project results	Project completion on time
	Stability of technological equipment
	The efficiency of the equipment used

	Possibility in usage

6.5.2. The organizational structure of the project.

This section discusses working group of this project, the role of each participant in this project, and the functions performed by each of the participants as well as their labor costs in the project. Table 9 shows working group of the project. In the course of the scientific project, in addition to the master's student, a number of specialists are involved:

* Project Manager - responsible for the implementation of the project within the specified resource constraints, coordinates the activities of the project participants. In most cases, this role is performed by the head of the master's thesis.

* Project executor- the master's student responsible for scientific research.

Table 9 – Working group of the project

Participant	Role in Position	Functions	Labor time, hours.
Mere P. A	Executor	Work on project implementation	77 days x 7hours
Ushakov I.A.	Consultant	Coordination of work activities and assistance in project implementation	48 days x 7 hours
Total			875 hrs.

6.6. Project Limitations.

Project limitations are all factors that can be as a restriction on the degree of freedom of the project team members.

Table 10 – Project Limitations and assumptions

Factor	Limitations/assumptions
1. Project budget	1,700,100 RUB
1.1 Source of budgeting	TPU, Laboratory for isotopic Analysis and Technologies
2. Project timeline:	1 February 2022 – 31 May 2022

Date of approval of the project management plan	1 February 2022
Date of pass of reactor	15 March 2022 – 31 May 2022
2.2 Project completion date	04 June 2022

As a result of the initialization of the project, the goals and expected results were formulated, the stakeholders of the project and the financial framework were identified, which is very important for the successful completion of the project and its implementation.

6.6.1. Planning of scientific and technical project management

The planning process group consists of the processes that are carried out to determine the overall content of the work, clarify the goals, and develop the sequence of actions required to achieve these goals. The scientific project management plan should include the following:

i. *Hierarchical structure of project activities:* Detailing the enlarged work structure. In the process of creating an HWS, the content of the entire project is structured and defined.
ii. *Deadlines for the project stages*: As part of planning a science project, you need to build a project timeline and a Gantt chart. Project schedule is in table 11.

Table 11. Project Schedule

№	Job title	Duration, working days	Start date	Date of completion	Participants
1	Development of technical assignments and calendar planning of research.	3 days	14/02/2022	16/02/2022	Consultant, Executor,
2	Place of the on-job performance at nuclear research reactor IRT-T	1 day	15/03/2022	15/03/2022	Consultant,

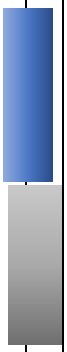
3	Literature review	10 days	16/03/2022	29/03/2022	Executor
4	Preliminary calculations, consultations, choosing working Equipments.	10 days	21/03/2022	29/04/2022	Executor, Consultant
5	Preparation of irradiation targets (Yb_2O_3 & Lu_2O_3)	5 days	04/04/2022	11/04/2022	Executor
6	- Production of Lu-177 - Separation of Lu from Yb targets, preparation of Yb_2Cl_3, $LuCl_3$, tracers	3 days	14/04/2022	18/04/2022	Consultant, Executor.
7	Preparation of cation exchange resin column resin column and flow test rate.	1 days	21/04/2022	21/04/2022	Consultant, Executor.
8	- Preparation of Non-radioactive Yb_2O_3 target and activation solution with tracer LuCl3, YbCl3, Hg. - Purification of radioactive activated aliquot solution. - Gamma spectrum analysis of aliquot.	4 days	25/04/2022	28/04/2022	Consultant, Executor.
9	Online consultations: - Gamma spectrum analysis results, - Detection of impurities by Neutron Activation Analysis - Pre-Defense Preparation	3 days	29/04/2022	3/05/2022	Consultant, Executor
10	Data and results analysis	2 days	4/05/2022	05/05/2022	Executor
11	Consultation for Pre-defense Presentation	3 days	06/05/2022	09/05/2022	Consultant /Executor
12	Pre-defense Preparation	5 days	06/05/2022	11/05/2022	Consultant, Executor
13	Pre- defense	1 day	12/05/2022	12/05/2022	Executor

14	Final thesis write-up	10 days	16/05/2022	27//05/2022	Consultant, Executor
15	Completion of thesis and submissions	1 5 days	16/05/2022	04/06/2022	Executor
16	Master's thesis defense	1 day	24/06/2022	24/06/2022	Executor
	Total days Executor	77 days			
	Total days: Supervisor	48 days			

Table 12 shows a Gantt chart, which is a type of bar chart that illustrates a project schedule. This chart lists the tasks to be performed on the vertical axis, and time intervals on the horizontal axis. The width of the horizontal bars in the graph shows the duration of each activity.

Table 12 - Gantt chart

№	Activities	Participant	T_c, days	Duration of the project																			
				February				March				April				May				June			
				1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	- General supervision, Calendar planning of research and technical assignments.	C	3																				
2	Familiarization with Nuclear research reactor IRT-T and radiochemistry labs	C	1																				
3	Literature review	E	10																				
4	Preliminary calculations, consultations, choosing working Equipments.	C, E	10																				
5	Preparation of irradiation targets (Yb_2O_3 & Lu_2O_3)	C, E	5																				

6	- Production of Lu-177 Separation of Lu from Yb targets, preparation of Yb_2Cl_3, $LuCl_3$, tracers	C, E	3	
7	Preparation of cation exchange resin column resin column and flow test rate.	C, E	1	
8	- Preparation of Non-radioactive Yb_2O_3 target and activation solution with tracer LuCl3, YbCl3, Hg. - Purification of radioactive activated aliquot solution. Gamma spectrum analysis of aliquot.	C, E	4	
9	Online consultations: - Gamma spectrum analysis results, - Detection of impurities by Neutron Activation Analysis Pre-Defense Preparation	C, E	3	
10	Data and results analysis	E	4	
11	Consultation for Pre-defense Preparation	C, E	3	
12	Pre-defense Preparation	E	3	
13	Pre- defense	E	1	
14	Final thesis write-up	E	10	

15	Completion of thesis and submission	C, E	15																					
16	Master's thesis defense	E																						

6.7. Scientific and technical research budget

When planning the budget of scientific research, it should be ensured that all types of planned expenditures necessary for its implementation are fully and reliably reflected. In the process of forming the budget, the planned costs are grouped according to the items presented in the table 13; following grouping of costs by items such as:

- Costs for raw materials, purchased parts and semi-finished goods;
- Costs for special equipment for scientific experiments;
- Expenses for the basic and add salaries of the theme performers;
- Costs for social security pays;
- Other direct costs;
- Energy cost;
- Overhead costs.

6.7.1. Calculation of cost material

This type includes the cost of all materials, raw materials, purchased components and semi-finished products used and consumed in the development of a research project. The value of material costs is calculated according to the current price lists or contractual prices. The value of material costs includes transportation and procurement costs (3-5 % of the price). The same article includes the costs of documentation processing (office supplies, ranking of materials). The results for this article are entered in Table 9.

The calculation of material costs may be also carried out according to the formula:

$$C_m = (1 + k_T) \cdot \sum_{i=1}^{m} P_i \cdot N_{consi}$$

where C_m - cost for raw materials, purchased parts and semi-finished goods, rubles;

m – the number of types of material resources consumed in the performance of scientific research;

N_{consi} – the amount of material resources of the i-th species planned to be used when performing scientific research (units, kg, m, m^2, etc.);

P_i – the acquisition price of a unit of the i-th type of material resources consumed (rub. /units, rub. /kg, rub. /m, rub. /m^2, etc.);

k_T – coefficient taking into account transportation costs.

Prices for material resources can be set according to data posted on relevant websites on the internet by manufacturers (or supplier organizations).

Table 13 - Costs for raw materials, purchased parts and semi-finished goods

Materials	Size of unit	Cost of material (Price per unit, rubles)	Quantity of material used	Sum, rubles (Total cost of material used)
Yb_2O_3 (powder)	10 g	6521,89	19.1 mg	12.45
Lu_2O_3 (powder)	5 g	24729,49	11.6 mg	57.97
Hydrochloric acid, 36.5 – 38%	500 ml	13884,43	40 ml	1110.75
Lewatit MonoPlus T214 ion exchange resin, macroporous	100 g	5785,05	1 g	57.85
Aluminum foil	1 roll	1851,22	1 roll	1550,83
Filter paper	500 EA	2728,11	3	316,13
Cotton wool	1 pack	65,8	1 pack	65,8
A4 printer paper	500	595.00	100	119
Pipette	1 EA	24419.02	1	24419.02
Measuring cylinder	2 EA	9743.25	2	9743,25
Flacon	60 EA	12544.43	4	836.89
Pipette tips	1000EA	9737.05	30	292.11

Chromatography Gravity column	1 EA	12239.96	1	12239.96
Glass beaker	4	3723.93	4	3729.93
Scissor	1 EA	852.53	1	852,53
Total costs for materials		73855,17		42875,93
Total costs of material used and considering transportation cost (5%), C_m				44075.93

6.7.2. Cost for special equipment for scientific experiments

This article includes all the costs associated with the purchase of special equipment (instruments, control and measuring equipment, stands, devices and mechanisms) necessary for carrying out work on a specific topic. The cost of special equipment is determined according to the current price lists, and in some cases at the agreed price.

Calculation of the Depreciation

Depreciation is not charged if an equipment cost is less than 40 thousand rubles; its cost is taken into account in full. If available equipment is used, then to calculate depreciation:

$$A = \frac{C_{initial} * \mathrm{H_a}}{100}$$

A - annual amount of depreciation; $C_{initial}$- initial cost of the equipment; $\mathrm{T_{сл}}$ - life expectancy

$\mathrm{H_a} = \frac{100}{\mathrm{T_{сл}}}$ - rate of depreciation;

Table 14a - *Depreciation* of special equipment

№	Equipment identification	Quantity of equipment	Total cost of equipment, rub.	Life expectancy, year	Depreciation for the duration of the project, rub.
1	Laptop	1	41,000.00	5	2,021.92
2	HPGe detector (GX1018 Canberra)	1	400,000.00	5	2,191.78
3	Heating Oven	1	150,000.00	10	82.19 ₽

4	Analytical laboratory scales		172,942.65	10	189.53
5	Cementation process Equipments	1	200,000.00	10	273.97
6	Electro-amalgamation equipment	1	100,150.00	10	54.88
7	Fume hood		85,290.00	10	233.67
8	Water distiller	1	60,000.00	10	49.32
9	Adjustable volume pipette	1	21,646.00	10	29.65
10	Drying oven	1	100,000.00	10	109.59
11	Retort stand	1	2,526.00	10	2.77
Tota1		-	1,333,554.65	-	5,239.26 ₽

6.7.3. Cost for basic and add salary

This article includes the basic salary of scientific and engineering workers, workers of model workshops and experimental production facilities directly involved in the performance of work on this topic. The amount of salary expenses is determined based on the labor intensity of the work performed and the current system of remuneration. The basic salary includes a bonus paid monthly from the salary fund (the amount is determined by the Regulations on Remuneration of Labor). The calculation of the basic salary is summarized in Table 17.

This section includes the basic salary of participants directly involved in the implementation of work on this research. The value of salary costs is determined based on the labor intensity of the work performed and the current salary system

The basic salary (S_b) is calculated according to the formula:

$$S_{\text{b}} = S_a \cdot T_{\text{w}},$$

where Sb – basic salary per participant; T_w – the duration of the work performed by the scientific and technical worker, working days; S_d - the average daily salary of a participant, rub.

The average daily salary is calculated by the formula:

$$S_d = \frac{S_m \cdot M}{F_v}$$

Where S_m – monthly salary of a participant, rub.; M – the number of months of work without leave during the year, months; at holiday in 48 days, M = 11.2 months, 6 day per week; F_v– valid annual fund of working time of scientific and technical personnel (251 days).

Table 11. The valid annual fund of working time

Working time indicators	Executor	Supervisor
Calendar number of days	365	365
The number of non-working days weekend holidays	- 52 14	- 52 14
Loss of working time - vacation - isolation period - sick absence	48 -	48 -
The valid annual fund of working time	251	251

Monthly salary is calculated by formula:

$$S_m = S_{base} \cdot \left(K_{prem} + K_{bon} + 1 \right) \cdot K_{reg}$$

where S_{base} – base salary, rubles;

K_{prem} – premium rate (equal 0,3);

K_{bon} – bonus rate (equal 0,25);

K_{reg} – regional rate (for Tomsk region is equal 1,3).

Table 12. Calculation of the basic salaries

Performers	S_{base}, Rubles	k_{bonus}	$k_{premium}$	k_{reg}	S_{month}, rub.	W_d, rub.	T_p, work days (from table	W_{base}, rub.
Consultant	358800.00	0,25	0,3	1,3	46540,00	1597,45	48	52715,85
Executor	8720				11336,00	642.53	77	50759,887
Total								103475.74

Basic salary

The basic salary is calculated according to the following formula:

$$W_{Base} = S_d \cdot T_w$$

where w_{base} – basic salary per participant;

T_w – the duration of the work performed by the scientific and technical worker, working days; S_d - the average daily salary of a participant, rub.

Additional salaries

The Additional salaries are calculated on the basis of 10-15% of the base salary of workers:

$$W_{add} = K_{Extra} \cdot W_{Base}$$

where W_{add}– additional salary, rubles; K_{Extra}– additional salary coefficient (10%),W_{base} additional salary, rubles;

Table 13 – Salary of scientific research project performers.

Executors	Salary	
	Basic	Additional

Consultant	52715,85	5727,59
Executor	50759,87	5057,99
Total payments at article C_{sal}		10785.58

Social security pays

Social security pays (so-called labor tax) to extra-budgetary funds are compulsory according to the norms established by the legislation of the Russian Federation to the state social insurance (SIF), pension fund (PF) and medical insurance (FCMIF) from the costs of workers.

Payment to extra-budgetary funds is determined of the formula:

$$P_{social} = k_b \cdot (W_{base} + W_{add}) \quad (9)$$

where k_b – coefficient of deductions for labor tax.

In accordance with the Federal law of July 24, 2009 No. 212-FL, the amount of insurance contributions is set at 30%. Institutions conducting educational and scientific activities have rate – 30.2%.

Table 15 - Labor tax

Coefficient of deductions	Consultant	Executor
Salary, rubles	5787,44	55835,86
Labor tax, rubles	1747.81	16862.43

6.8. Scientific and industrial business trips

This article includes the travel expenses of scientific and production personnel associated with the direct implementation of a scientific research project, the amount of which

is assumed to be 10% of the main and additional salaries of all personnel engaged in the implementation of this topic.

6.8.1. Pays for work performed by other firms

This item includes the cost of counterparty work, i.e. work performed by third-party organizations and enterprises on the order of this scientific and technical organization, the results of which are used in a scientific research project. In addition, this item of expenditure includes the payment of consultations, the use of the Internet, etc. The amount of these costs is determined according to the contractual terms.

6.8.2. Overhead costs

Overhead costs include other management and maintenance costs that can be allocated directly to the project. In addition, this includes expenses for the maintenance, operation and repair of equipment, production tools and equipment, buildings, structures, etc.

Overhead costs account from 30% to 90% of the amount of basic and additional salary of employees.

Overhead is calculated according to the formula:

$$C_{ov} = k_{ov} \cdot (W_{base} + W_{add})$$

where k_{ov} – overhead rate.

Table 16 - Overheads cost

	Consultant	Executor
Overhead rate	40%	
Salary, rubles	57987,44	55835,86
Overhead, rubles	23194,98	22334,34
Total	45529.32	

Other directed costs

Energy cost for equipment calculated using the formula:

$$C = P_{el} \cdot P \cdot F_{eq}$$

where: P_{el} is the power rate (5.8 rubles per kWh)

P is the power of equipment

F_{eq} is the equipment usage time

Table 17 – other directed costs

	Power rates, kWh	Power of equipment, kW	Equipment usage time, hr	Energy cost, rubles
HPGe detector (GX1018 Canberra)	5.8	0.5	480	1392
Cementation equipment	5.8	0.5	24	69,60
Total				1461,60

6.9. Determination of resource (resource-saving), financial, budgetary, social and economic efficiency of research

The effectiveness of a scientific resource-saving project includes social efficiency, economic and budgetary efficiency. Public efficiency indicators take into account the socio-economic consequences of the implementation of an investment project for society as a whole, including the direct results and costs of the project, as well as costs and benefits in related sectors of the economy, environmental, social and other non-economic effects.

The indicators of the economic efficiency of the project take into account the financial implications of its implementation for the enterprise implementing the project. In this case, the performance indicators of the project as a whole characterize from an economic point of view, technical, technological and organizational design solutions.

Budgetary efficiency is characterized by the participation of the state in the project in terms of expenditures and revenues of budgets of all levels.

In addition to the above types of efficiency, the resource effect can be distinguished (characterized by indicators reflecting the influence of innovation on the volume of production and consumption of one or another type of resource), scientific and technical (evaluated by indicators of novelty and usefulness), etc.

6.9.1. Formation of the budget for the costs of a research project

After carrying out cost calculations for all budget items, the lower limit of the cost of project development can be determined. The definition of the cost budget for the research project for each implementation option is calculated in table 18.

Table 18 – Formation of budget for the research cost

Name of article	Sum, rub.
Costs for raw materials, purchased parts and semi-finished goods	1,428,554.65
Cost for depreciation of the special equipment for the duration of the project	5,239.26
Cost for basic salary	103475.74
Cost for additional salary	10785.58
Cost for social security pays (Labor tax)	18610.24
Overhead cost	45529.32
Other directed cost	69,984.78
Total (personal research if equipment had to be bought)	1,682,179.57
Total(current)	348624.92

Total project costs amounted to 1,682,179.57 rubles if the research was done in a real-life scenario, but if you subtract the cost of the special equipment that I freely used which are owned by the university the cost will drop down to 348624.92.

6.10. Evaluation of the Absolute Effectiveness of the Project

Determination of efficiency is based on the calculation of the integral indicator of the efficiency of scientific research. Its finding is associated with the determination of two weighted averages: financial efficiency and resource efficiency. An integral indicator of the financial efficiency of scientific research is obtained in assessing the budget of costs of three (or more) variants of the implementation of scientific research. For this, the largest integral indicator of the implementation of a technical problem is taken as the basis of the calculation (as the denominator), with which the financial values for all execution options are correlated.

$$I_f^p = \frac{F_{p_i}}{F_{max}}$$

where I_f^p – integral financial indicator of current project;

F_{p_i} – price of i-th variant of execution;

F_{max} – the maximum cost of execution of the research project (including analogues).

The resulting value of the integral financial indicator of development reflects the corresponding numerical increase in the budget of development costs in times (a value greater than one), or the corresponding numerical reduction in the cost of development in times (a value less than one, but higher than zero).

In this project, $F_{p_i} = 1682{,}179.57$ It is assumed that, $F_{max} = 450000$.

Hence, the integral financial indicator is:

$$I_f^p = \frac{1{,}682{,}179.57}{450000} = 3.74$$

$$I_f^p = \frac{F_{p_i}}{F_{max}} = \frac{450000}{450000} = 1$$

The integral indicator of the resource efficiency of the variants of the object of research can be defined as follows:

$$I_m^a = \sum_{i=1}^{n} a_i b_i^a \quad , \quad I_m^p = \sum_{i=1}^{n} a_i b_i^p \quad , \qquad (13)$$

where

I_m^a is an integral indicator of resource efficiency of options;

a_i- the weight coefficient of the i-th parameter;

b_i^a, b_i^p - the score of the i-th parameter for the analog and development, set by an expert method on the selected rating scale;

n - the number of comparison parameters.

It is recommended to calculate the integral resource efficiency indicator shown in table 17.

Table 17 – Comparative assessment of the characteristics of the project execution options. implementation options

Criteria	Parameter weighing factor	Current project	Analog 1 Cation Exchange Resin Purification methods
Growth in User' productivity	0.2	4	5
Production and separation method	0,3	5	4
Safety and degree of Impurities	0.3	5	4
Reliability	0.2	4	4
Total	1	4,5 (average)	4.25 (average)

$$I_m^a = (0.2 \cdot 4) + (0.3 \cdot 5) + (0.3 \cdot 5) + (0.2 \cdot 4) = 4.6$$

$$Analogs\ 1 = (0.2 \cdot 5) + (0.3 \cdot 4) + (0.3 \cdot 4) + (0.2 \cdot 4) = 4.2$$

The integrated index of efficiency of scientific research project (I_{fin}^{p}) and analogues (I_{fin}^{af}) is determined on the basis of the integrated index of resource efficiency and integrated financial index by formulas:

$$I_{fin}^{p} = \frac{I_{m}^{p}}{I_{f}^{p}} = \frac{4,6}{3,84} = 1.30$$

$$I_{fin}^{a1} = \frac{I_{f}^{a1}}{I_{f}^{p}} = \frac{4.2}{1} = 4.2$$

Comparison of the integral performance indicator of the current project and its analogues will allow to determine the comparative efficiency of the project shown in table 18.

Comparative effectiveness of the project:

$$C_{eff} = \frac{I_{fin}^{p}}{I_{m}^{p}} = \frac{4.6}{3.60} = 1.30$$

Table 18 – Comparative efficiency of the project

№	Indicator	Project	Analog
1	Integral financial indicator	3,84	1
2	Integral resource efficiency indicator	4.6	4.2
3	Integral efficiency indicator	1.30	1
4	Comparative evaluation of the project execution variants	1.30	1

Comparison of the values of integral indicators of efficiency allows master's students to choose a more effective solution to the technical problem in the master's thesis basing on financial and resource efficiency.

Conclusion

Thus, in this section was developed stages for design and create competitive development that meet the requirements in the field of resource efficiency and resource saving.

These stages include:

- development of a common economic project idea, formation of a project concept;
- organization of work on a research project;
- identification of possible research alternatives;
- research planning;
- assessing the commercial potential and prospects of scientific research from the standpoint of resource efficiency and resource saving;
- determination of resource (resource saving), financial, budget, social and economic efficiency of the project.

In the course of performing the economic part of the qualification master work, calculations were made of the planned cost of research and the time spent. The total cost of work would have been 1682,179.57 rubles, the main component that would contribute to the cost of the scientific and technical research was the equipment cost. Since the cost of the equipment was not incurred in this study the cost was 34,8624.92.

References

[1] WHO, “Cancer.” https://www.who.int/health-topics/cancer#tab=tab_1 (accessed Mar. 30, 2022).

[2] “Cancer Imaging Basics | Cancer Imaging Program (CIP),” Nov. 06, 2020. https://imaging.cancer.gov/imaging_basics/cancer_imaging.htm (accessed Apr. 07, 2022).

[3] C. Grupen, “A table of frequently used radioisotopes,” in *Introduction to Radiation Protection: Practical Knowledge for Handling Radioactive Sources*, European Organization for Nuclear Research (CERN), 2010. Accessed: Mar. 31, 2022. [Online]. Available: https://cds.cern.ch/record/1309915/files/978-3-642-02586-0_BookBackMatter.pdf

[4] Florina-Gianina Elfarra, Radu Mutihac, and Ileana Radulescu, “Thyroid scintigraphy using Technetium-99m,” 2021. https://www.rad-conference.org/RAD_2021_Book_of_Abstracts.pdf#page=222 (accessed Jun. 01, 2022).

[5] C. Bisschop, E. C. de Heer, A. H. Brouwers, G. A. P. Hospers, and M. Jalving, “Rational use of 18F-FDG PET/CT in patients with advanced cutaneous melanoma: A systematic review,” *Critical Reviews in Oncology/Hematology*, vol. 153, p. 103044, Sep. 2020, doi: 10.1016/J.CRITREVONC.2020.103044.

[6] A. Dash, M. R. A. Pillai, and F. F. Knapp, “Production of 177Lu for Targeted Radionuclide Therapy: Available Options,” *Nuclear Medicine and Molecular Imaging*, vol. 49, no. 2, p. 85, Jun. 2015, doi: 10.1007/S13139-014-0315-Z.

[7] “Production, Quality Control and Clinical Applications of Radiosynovectomy agents IAEA Technical Report Series,” 2019.

[8] F. B. Payolla, A. C. Massabni, and C. Orvig, “Radiopharmaceuticals for diagnosis in nuclear medicine: A short review,” *Ecletica Quimica*, vol. 44, no. 3, pp. 11–19, 2019, doi: 10.26850/1678-4618EQJ.V44.3.2019.P11-19.

[9] G. Currie, J. Wheat, R. Davidson, and H. Kiat, “Radionuclide production,” *Radiographer*, vol. 58, no. 3, pp. 46–52, Sep. 2011, doi: 10.1002/J.2051-3909.2011.TB00155.X.

[10] S. Pathmanandavel *et al.*, “177Lu-PSMA-617 and Idronoxil in Men with End-Stage Metastatic Castration-Resistant Prostate Cancer (LuPIN): Patient Outcomes and Predictors of Treatment Response in a Phase I/II Trial.,” *J Nucl Med*, vol. 63, no. 4, pp. 560–566, Apr. 2022, doi: 10.2967/jnumed.121.262552.

[11] I. Kambali, “Production of Lu-177 Radionuclide using Deuteron Beams: Comparison between (d,n) and (d,p) Nuclear Reactions,” *Journal of Physics: Conference Series*, vol. 1120, no. 1, Dec. 2018, doi: 10.1088/1742-6596/1120/1/012011.

[12] A. Dash, F. F. Knapp, and M. Pillai, “Targeted Radionuclide Therapy - An Overview,” *Current Radiopharmaceuticals*, vol. 6, no. 3, pp. 152–180, Apr. 2014, doi: 10.2174/18744710113066660023.

[13] T. G. Chan, E. O’neill, C. Habjan, and B. Cornelissen, “Combination Strategies to Improve Targeted Radionuclide Therapy,” 2020, doi: 10.2967/jnumed.120.248062.

[14] M. Sathekge and M. B. Chb, “Targeted radionuclide therapy Targeted radionuclide therapy has the potential to selectively deliver radiation to diseased cells with minimal toxicity to surrounding tissues,” *CME August*, vol. 31, no. 8, p. 289, 2013, Accessed: Apr. 10, 2022. [Online]. Available: https://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/1335/809/targetedradionuclidetherapy_sathekge.pdf

[15] “PRODUCT MONOGRAPH LUTATHERA ® LUTETIUM (177 LU) OXODOTREOTIDE FORMER”.

[16] J. Strosberg *et al.*, “Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors,” *N Engl J Med*, vol. 376, no. 2, pp. 125–135, Jan. 2017, doi: 10.1056/NEJMOA1607427.

[17] Advanced Accelerator Applications, “A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours - Full Text View - ClinicalTrials.gov,” 2022. Accessed: Apr. 09, 2022. [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT01578239#studydesc

[18] Matthew Stenger, “Lutetium Lu-177 Dotatate in Gastroenteropancreatic Neuroendocrine Tumors - The ASCO Post,” Mar. 10, 2018. https://ascopost.com/issues/march-10-2018/lutetium-lu-177-dotatate-in-gastroenteropancreatic-neuroendocrine-tumors/ (accessed Apr. 09, 2022).

[19] F. Sundquist *et al.*, “A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of 177Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-Risk Neuroblastoma-LuDO-N.,” *Front Pediatr*, vol. 10, p. 836230, Mar. 2022, doi: 10.3389/fped.2022.836230.

[20] J. Capdevila *et al.*, “Position Statement on the Diagnosis, Treatment, and Response Evaluation to Systemic Therapies of Advanced Neuroendocrine Tumors, With a Special Focus on Radioligand Therapy.,” *Oncologist*, vol. 27, no. 4, pp. e328–e339, Apr. 2022, doi: 10.1093/oncolo/oyab041.

[21] J. R. Strosberg *et al.*, “177Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial,” *The Lancet Oncology*, vol. 22, no. 12, pp. 1752–1763, Dec. 2021, doi: 10.1016/S1470-2045(21)00572-6.

[22] FDA and CDER, “ Lutathera (lutetium Lu 177 dotatate) injection prescribing information,” Jan. 2018, Accessed: Apr. 09, 2022. [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf

[23] M. Asti *et al.*, "Methods for preparation and administration of lutetium-177 oxodotreotide 3.7 GBq: proceedings from an Italian advisory board," *Clinical and Translational Imaging*, vol. 9, no. 4, pp. 277–280, Aug. 2021, doi: 10.1007/S40336-021-00431-2.

[24] L. L. Radford and S. E. Lapi, "Methods for the Production of Radionuclides for Medicine," *Radiopharmaceutical Chemistry*, pp. 63–83, 2019, doi: 10.1007/978-3-319-98947-1_4.

[25] IAEA, "Manual for reactor produced radioisotopes. IAEA-TECDOC-1340," 2003, Accessed: Mar. 30, 2022. [Online]. Available: https://www-pub.iaea.org/MTCD/publications/PDF/te_1340_web.pdf

[26] "Manual for reactor produced radioisotopes," 2003.

[27] J. Poder, R. Smith, and A. Haworth, "Low-dose-rate iodine-125 seed air kerma strength measurement intercomparison," *Brachytherapy*, vol. 19, no. 1, pp. 119–125, Jan. 2020, doi: 10.1016/j.brachy.2019.10.001.

[28] IAEA, "TRS. NO 465 Cyclotron Produced Radionuclides: Principles and Practice," *INTERNATIONAL ATOMIC ENERGY AGENCY VIENNA*, 2008. https://www-pub.iaea.org/MTCD/publications/PDF/trs465_web.pdf (accessed Apr. 01, 2022).

[29] Z. Dvorakova, "Production and chemical processing of 177Lu for nuclear medicine at the Munich research reactor FRM-II".

[30] M. R. A. Pillai, S. Chakraborty, T. Das, M. Venkatesh, and N. Ramamoorthy, "Production logistics of 177Lu for radionuclide therapy," *Applied Radiation and Isotopes*, vol. 59, no. 2–3, pp. 109–118, 2003, doi: 10.1016/S0969-8043(03)00158-1.

[31] "Practical Aspects of Operating A Neutron Activation Analysis Laboratory | IAEA." https://www.iaea.org/publications/820/practical-aspects-of-operating-a-neutron-activation-analysis-laboratory (accessed Jun. 03, 2022).

[32] A. Luca, M. Sahagia, M. R. Ioan, A. Antohe, and B. L. Savu, "Experimental determination of some nuclear decay data in the decays of (177)Lu, (186)Re and

(124)I," *Appl Radiat Isot*, vol. 109, pp. 146–150, Mar. 2016, doi: 10.1016/J.APRADISO.2015.11.072.

[33] S. Chakraborty *et al.*, "Barium titanate microparticles as potential carrier platform for lanthanide radionuclides for their use in the treatment of arthritis," *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 61, no. 7, pp. 522–532, Jun. 2018, doi: 10.1002/JLCR.3615.

[34] J. Blakkisrud, "Dosimetry in patients treated with 177Lu[Lu-Lilotomab Satetraxetan]," pp. 13–15, 2022, Accessed: Apr. 20, 2022. [Online]. Available: https://www.duo.uio.no/bitstream/handle/10852/91402/1/PhD-Blakkisrud-2022.pdf

[35] M. Vorster *et al.*, "South African guidelines for receptor radioligand therapy (RLT) with Lu-177-PSMA in prostate cancer," *South African Journal of Surgery*, vol. 57, no. 4, pp. 45–51, 2019, doi: 10.17159/2078-5151/2019/V57N4A3107.

[36] M. A. Kellett, "177Lu: DDEP Evaluation of the decay scheme for an emerging radiopharmaceutical," *Applied Radiation and Isotopes*, vol. 109, pp. 129–132, Mar. 2016, doi: 10.1016/J.APRADISO.2015.11.057.

[37] A. K. Miyahira *et al.*, "Meeting report from the Prostate Cancer Foundation PSMA theranostics state of the science meeting," *Prostate*, vol. 80, no. 15, pp. 1273–1296, Nov. 2020, doi: 10.1002/PROS.24056.

[38] U. Hennrich and K. Kopka, "Lutathera®: The first FDA-and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy," *Pharmaceuticals*, vol. 12, no. 3, Sep. 2019, doi: 10.3390/PH12030114.

[39] M. S. Hofman *et al.*, "[177 Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study," *The Lancet Oncology*, vol. 19, no. 6, pp. 825–833, Jun. 2018, doi: 10.1016/S1470-2045(18)30198-0.

[40] S. T. Tagawa *et al.*, "Phase 1/2 study of fractionated dose lutetium-177–labeled anti–prostate-specific membrane antigen monoclonal antibody J591 (177Lu-J591) for

metastatic castration-resistant prostate cancer," *Cancer*, vol. 125, no. 15, pp. 2561–2569, Aug. 2019, doi: 10.1002/cncr.32072.

[41] R. Mikolajczak, N. P. van der Meulen, and S. E. Lapi, "Radiometals for imaging and theranostics, current production, and future perspectives," *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 62, no. 10, pp. 615–634, Aug. 2019, doi: 10.1002/JLCR.3770.

[42] Isotopes Technologies Garching GmbH, "ITG Lu-177 n.c.a." Accessed: May 30, 2022. [Online]. Available: https://www.diagimaging.com/literature/ITG/ITG%20Lu-177%20n.c.a.pdf

[43] A. Golabian, M. A. Hosseini, M. Ahmadi, B. Soleimani, and M. Rezvanifard, "The feasibility study of 177Lu production in Miniature Neutron Source Reactors using a multi-stage approach in Isfahan, Iran," *Applied Radiation and Isotopes*, vol. 131, pp. 62–66, Jan. 2018, doi: 10.1016/J.APRADISO.2017.11.019.

[44] R. Bhardwaj, B. Ponsard, M. Sarilar, B. Wolterbeek, A. Denkova, and P. Serra-Crespo, "Large-scale production of lutetium-177m for the 177mLu/177Lu radionuclide generator," *Applied Radiation and Isotopes*, vol. 156, p. 108986, Feb. 2020, doi: 10.1016/J.APRADISO.2019.108986.

[45] S. Chakraborty, K. v. Vimalnath, S. P. Lohar, P. Shetty, and A. Dash, "On the practical aspects of large-scale production of177Lu for peptide receptor radionuclide therapy using direct neutron activation of176Lu in a medium flux research reactor: The Indian experience," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 302, no. 1, pp. 233–243, Oct. 2014, doi: 10.1007/S10967-014-3169-Z/FIGURES/9.

[46] K. v. Vimalnath *et al.*, "Aspects of yield and specific activity of (n,γ) produced 177Lu used in targeted radionuclide therapy," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 302, no. 2, pp. 809–812, Oct. 2014, doi: 10.1007/S10967-014-3240-9/FIGURES/1.

[47] P. P. Boldyrev, A. v Kurochkin, R. F. Nurtdinov, M. A. Proshin, D. Yu Chuvilin, and Y. A. Yashin, "Electrochemical Method for Producing Radionuclide Lu-177 with High

Specific Activity," vol. 71, no. 3, pp. 184–190, 2016, doi: 10.3103/S0027131416030032.

[48] T. W. Miller, "Production of Lutetium-177 via the Indirect Route Using PUR-1," May 2021, doi: 10.25394/PGS.14502777.V1.

[49] A. Bilewicz, K. Żuchowska, and B. Bartoś, "Separation of Yb as YbSO 4 from the 176 Yb target for production of 177 Lu via the 176 Yb(n, γ) 177 Yb→ 177 Lu process," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 280, no. 1, pp. 167–169, 2009, doi: 10.1007/S10967-008-7437-7.

[50] N. A. Lebedev, A. F. Novgorodov, R. Misiak, J. Brockmann, and F. Rösch, "Radiochemical separation of no-carrier-added 177Lu as produced via the 176Yb(n,gamma)177Yb-->177Lu process," *Appl Radiat Isot*, vol. 53, no. 3, pp. 421–425, Sep. 2000, doi: 10.1016/S0969-8043(99)00284-5.

[51] "TPU began to produce lutetium isotopes for treatment of cancer - РИА Томск." https://www.riatomsk.ru/article/20190828/tpu-began-to-produce-lutetium-isotopes-for-treatment-of-cancer/ (accessed Jun. 03, 2022).

[52] "SAFARI-1 - NTP." https://www.ntp.co.za/safari-1/ (accessed Jun. 03, 2022).

[53] S. Maage and O. Knoesen, "Radiation aspects related to high and low specific activity 177Lu and its significance to peptide receptor radiation therapy," *Physica Medica*, vol. 31, p. S16, Sep. 2015, doi: 10.1016/J.EJMP.2015.07.066.

[54] S.M. Qaim, Forschungszentrum Jülich GmbH, and Jülich, "COMPARISON OF REACTOR AND CYCLOTRON PRODUCTION OF MEDICALLY IMPORTANT RADIOISOTOPES, WITH SPECIAL REFERENCE TO 99Mo/99mTc, 64,67Cu AND 103Pd," *IAEA TRS no 455*. https://www-pub.iaea.org/MTCD/publications/PDF/TRS455_web.pdf (accessed Apr. 02, 2022).

[55] R. Chakravarty and S. Chakraborty, "A review of advances in the last decade on targeted cancer therapy using 177Lu: focusing on 177Lu produced by the direct neutron activation route," *American Journal of Nuclear Medicine and Molecular Imaging*, vol.

11, no. 6, p. 443, 2021, Accessed: Apr. 24, 2022. [Online]. Available: /pmc/articles/PMC8727880/

[56] S. A. Hoedl and W. D. Updegraff, “The Production of Medical Isotopes without Nuclear Reactors or Uranium Enrichment On-Line Supplement”, Accessed: Apr. 01, 2022. [Online]. Available: https://scienceandglobalsecurity.org/archive/sgs23hoedl_app.pdf

[57] A. Hermanne, S. Takacs, M. B. Goldberg, E. Lavie, Y. N. Shubin, and S. Kovalev, “Deuteron-induced reactions on Yb: Measured cross sections and rationale for production pathways of carrier-free, medically relevant radionuclides,” *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, vol. 247, no. 2, pp. 223–231, Jun. 2006, doi: 10.1016/J.NIMB.2006.03.008.

[58] S. Manenti *et al.*, “Excitation function for deuteron induced nuclear reactions on natural ytterbium for production of high specific activity 177gLu in no-carrier-added form for metabolic radiotherapy,” *Applied Radiation and Isotopes*, vol. 69, no. 1, pp. 37–45, Jan. 2011, doi: 10.1016/J.APRADISO.2010.08.008.

[59] M. U. Khandaker, H. Haba, and H. A. Kassim, “Production of 177Lu, a potential radionuclide for diagnostic and therapeutic applications,” *AIP Conference Proceedings*, vol. 1657, no. 1, p. 120003, Apr. 2015, doi: 10.1063/1.4915229.

[60] I. Kambali, “Production of Lu-177 Radionuclide using Deuteron Beams: Comparison between (d,n) and (d,p) Nuclear Reactions,” *Journal of Physics: Conference Series*, vol. 1120, no. 1, p. 012011, Nov. 2018, doi: 10.1088/1742-6596/1120/1/012011.

[61] A. Bilewicz, K. Żuchowska, and B. Bartoś, “Separation of Yb as YbSO 4 from the 176 Yb target for production of 177 Lu via the 176 Yb(n, γ) 177 Yb → 177 Lu process,” *Journal of Radioanalytical and Nuclear Chemistry*, vol. 280, no. 1, pp. 167–169, 2009, doi: 10.1007/s10967-008-7437-7.

[62] A. Dash, R. Chakravarty, F. (Russ) Knapp, and A. Pillai, “Indirect Production of No Carrier Added (NCA) ^{177}Lu from Irradiation of Enriched ^{176}Yb: Options for

Ytterbium/Lutetium Separation," *Current Radiopharmaceuticals*, vol. 8, no. 2, pp. 107–118, Aug. 2015, doi: 10.2174/1874471008666150312161942.

[63] U. J. Park, J. S. Lee, K. H. Choi, S. S. Nam, and K. H. Yu, "Lu-177 preparation for radiotherapy application," *Applied Radiation and Isotopes*, vol. 115, pp. 8–12, Sep. 2016, doi: 10.1016/j.apradiso.2016.05.028.

[64] V. Tarasov, O. Andreev, E. Romanov, R. Kuznetsov, V. Kupriyanov, and I. Tselishchev, "Production of No-Carrier Added Lutetium-177 by Irradiation of Enriched Ytterbium-176," *Current Radiopharmaceuticals*, vol. 8, no. 2, pp. 95–106, Aug. 2015, doi: 10.2174/1874471008666150312160855.

[65] N. Salek, S. Shirvani Arani, A. Bahrami Samani, S. Vosoghi, and M. Mehrabi, "Feasibility study for production and quality control of Yb-175 as a byproduct of no carrier added Lu-177 preparation for radiolabeling of DOTMP," *Australasian Physical and Engineering Sciences in Medicine*, vol. 41, no. 1, pp. 69–79, Mar. 2018, doi: 10.1007/S13246-017-0611-X/FIGURES/10.

[66] J. K. Marsh, " Rare-earth metal amalgams. Part I. The reaction between sodium amalgam and rare-earth acetate and chloride solutions," *Journal of the Chemical Society (Resumed)*, no. 0, pp. 398–401, Jan. 1942, doi: 10.1039/JR9420000398.

[67] J. K. Marsh, "Rare-earth metal amalgams. Part II. The separation of neodymium, samarim, and gadolinium," *Journal of the Chemical Society (Resumed)*, no. 0, pp. 523–526, Jan. 1942, doi: 10.1039/JR9420000523.

[68] J. K. Marsh, "Rare-earth metal amalgams. Part III. The separation of ytterbium from its neighbours," *Journal of the Chemical Society (Resumed)*, no. 0, pp. 8–10, Jan. 1943, doi: 10.1039/JR9430000008.

[69] J. K. Marsh, "Rare-earth metal amalgams. Part IV. The isolation of europium," *Journal of the Chemical Society (Resumed)*, no. 0, pp. 531–535, Jan. 1943, doi: 10.1039/JR9430000531.

[70] C. Barkhausen, "Production of non carrier added (n.c.a.) 177 Lu for radiopharmaceutical applications," 2011.

https://www.semanticscholar.org/paper/Production-of-non-carrier-added-(n.c.a.)-177-Lu-for-Barkhausen/9ee618947d8aaf383cf6a881f7b7abab3f278473 (accessed Apr. 04, 2022).

[71] N. A. Lebedev, A. F. Novgorodov, R. Misiak, J. Brockmann, and F. Rösch, "Radiochemical separation of no-carrier-added 177Lu as produced via the 176Ybn,γ177Yb→177Lu process," *Applied Radiation and Isotopes*, vol. 53, no. 3, pp. 421–425, Sep. 2000, doi: 10.1016/S0969-8043(99)00284-5.

[72] S. Chakraborty, K. v. Vimalnath, S. P. Lohar, P. Shetty, and A. Dash, "On the practical aspects of large-scale production of177Lu for peptide receptor radionuclide therapy using direct neutron activation of176Lu in a medium flux research reactor: The Indian experience," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 302, no. 1, pp. 233–243, Oct. 2014, doi: 10.1007/S10967-014-3169-Z/FIGURES/9.

[73] R. Chakravarty, T. Das, A. Dash, and M. Venkatesh, "An electro-amalgamation approach to isolate no-carrier-added 177Lu from neutron irradiated Yb for biomedical applications," *Nucl Med Biol*, vol. 37, no. 7, pp. 811–820, Oct. 2010, doi: 10.1016/J.NUCMEDBIO.2010.04.082.

[74] S. Nafise, S. Mojtaba, G. M. Mohammad, S. A. Simindokht, and Ali Bahrami Samani, "Comparative studies of extraction chromatography and electro-amalgamation separation to produce no-carrier added 177Lu by Tehran research reactor," *Iranian Journal of Nuclear Medicibe*, 2017, Accessed: Apr. 21, 2022. [Online]. Available: https://irjnm.tums.ac.ir/article_23084.html

[75] P. P. Boldyrev, A. v Kurochkin, R. F. Nurtdinov, M. A. Proshin, D. Yu Chuvilin, and Y. A. Yashin, "Electrochemical Method for Producing Radionuclide Lu-177 with High Specific Activity," vol. 71, no. 3, pp. 184–190, 2016, doi: 10.3103/S0027131416030032.

[76] V. Tarasov, O. Andreev, E. Romanov, R. Kuznetsov, V. Kupriyanov, and I. Tselishchev, "Production of No-Carrier Added Lutetium-177 by Irradiation of Enriched

Ytterbium-176," *Current Radiopharmaceuticals*, vol. 8, no. 2, pp. 95–106, Aug. 2015, doi: 10.2174/1874471008666150312160855.

[77] N. Salek *et al.*, "Production, quality control, and determination of human absorbed dose of no carrier added 177Lu-risedronate for bone pain palliation therapy," *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 60, no. 1, pp. 20–29, Jan. 2017, doi: 10.1002/JLCR.3466.

[78] S. Watanabe *et al.*, "Production of highly purified no-carrier-added 177Lu for radioimmunotherapy," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 303, no. 1, pp. 935–940, Jan. 2015, doi: 10.1007/S10967-014-3534-Y.

[79] S. Happel, "An overview over some new extraction chromatographic resins and their application in radiopharmacy TrisKem International".

[80] "Novel Separation Materials Method Development Specialty Ion Exchange Resins Extraction Chromatographic Resins EXTRACTION CHROMATOGRAPHY Technical Documentation-Radiopharmacy", Accessed: Jun. 03, 2022. [Online]. Available: www.triskem.com

[81] N. A. Lebedev, A. F. Novgorodov, R. Misiak, J. Brockmann, and F. Rösch, "Radiochemical separation of no-carrier-added 177Lu as produced via the 176Yb(n,γ)177Yb→177Lu process," *Applied Radiation and Isotopes*, vol. 53, no. 3, pp. 421–425, Sep. 2000, doi: 10.1016/S0969-8043(99)00284-5.

[82] Z. Hubicki, "APPLICATION OF LEWATIT MONOPLUS MP-500 IN PRECONCENTRATION OF PALLADIUM(II) IONS FROM HYDROCHLORIC ACID-SODIUM CHLORIDE SOLUTIONS".

[83] "LEWATIT® MonoPlus TP 214." https://lanxess.com/en/Products-and-Solutions/Products/l/LEWATIT--MonoPlus-TP-214 (accessed Jun. 03, 2022).

[84] L. A. Hamidatou, "Overview of Neutron Activation Analysis," *Advanced Technologies and Applications of Neutron Activation Analysis*, Mar. 2019, doi: 10.5772/INTECHOPEN.85461.

[85] A. Dash, M. R. A. Pillai, and F. F. Knapp, “Production of (177)Lu for Targeted Radionuclide Therapy: Available Options,” *Nucl Med Mol Imaging*, vol. 49, no. 2, pp. 85–107, Jun. 2015, doi: 10.1007/S13139-014-0315-Z.

[86] S. Banerjee, M. R. A. Pillai, and F. F. Knapp, “Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications,” *Chem Rev*, vol. 115, no. 8, pp. 2934–2974, Apr. 2015, doi: 10.1021/CR500171E.

[87] R. Chakravarty and S. Chakraborty, “A review of advances in the last decade on targeted cancer therapy using 177Lu: focusing on 177Lu produced by the direct neutron activation route,” *American Journal of Nuclear Medicine and Molecular Imaging*, vol. 11, no. 6, p. 443, 2021, Accessed: Apr. 03, 2022. [Online]. Available: /pmc/articles/PMC8727880/

[88] D. van Dong *et al.*, “The Annual Report for 2013, VINATOM STUDY ON PREPARATION OF 177 Lu, LABELING WITH DOTATATE FOR USING IN DIAGNOSIS AND TREATMENT NEUROENDOCRINE TUMORS”.

[89] S. Roohi, S. K. Rizvi, and S. A. R. Naqvi, “177Lu-DOTATATE Peptide Receptor Radionuclide Therapy: Indigenously Developed Freeze Dried Cold Kit and Biological Response in In-Vitro and In-Vivo Models.,” *Dose Response*, vol. 19, no. 1, p. 1559325821990147, Feb. 2021, doi: 10.1177/1559325821990147.

[90] “IRT-T Nuclear Research Reactor - Reactor.” https://portal.tpu.ru/reactor/eng/reactor (accessed May 06, 2022).

[91] M. v. Shchurovskaya *et al.*, “Control rod calibration simulation using Monte Carlo code for the IRT-type research reactor,” *Annals of Nuclear Energy*, vol. 96, pp. 332–343, Oct. 2016, doi: 10.1016/J.ANUCENE.2016.06.015.

[92] “Gamma-Ray Spectroscopy | Nuclear Reactor Laboratory.” https://reactor.osu.edu/gamma-ray-spectroscopy (accessed Jun. 03, 2022).

[93] “Basic Sanitary Regulations for Radiation Safety (OSPORB-99/2010) Sanitary rules and regulations SP 2.6.1.2612-10,” Apr. 26, 2010. https://docs.cntd.ru/document/902214068?marker=6540IN (accessed May 17, 2022).

[94] C. Stoiber, A. Baer, N. Pelzer, and W. Tonhauser, “Handbook on Nuclear Law”, Accessed: Apr. 15, 2022. [Online]. Available: https://www-pub.iaea.org/mtcd/publications/pdf/pub1160_web.pdf

[95] “Russian Federation. LABOR CODE OF THE RUSSIAN FEDERATION OF 31 DECEMBER 2001.” https://www.ilo.org/dyn/natlex/docs/WEBTEXT/60535/65252/E01RUS01.htm#chap16 (accessed Apr. 13, 2022).

[96] “SanPiN 2.2.2/2.4.1340-03HYGIENIC REQUIREMENTS FOR PERSONAL ELECTRONIC COMPUTERS AND ORGANIZATION OF WORK | Eco - Electronics.” https://eco-e.ru/poleznoe/dokumentyi/gigienicheskie-trebovaniya-k-personalnyim-elektronno-vyichislitelnyim-mashinam-i-organizaczii-rabotyi/ (accessed May 16, 2022).

[97] “Federal Law of the Russian Federation ‘About use of atomic energy.’” https://cis-legislation.com/document.fwx?rgn=1628#A000000023 (accessed May 16, 2022).

[98] “SanPiN 2.2.4.548-96 Hygienic requirements to occupational microclimate.” https://www.russiangost.com/p-17057-sanpin-224548-96.aspx (accessed May 17, 2022).

[99] “SN 2.2.4 / 2.1.8.562-96 ‘Noise at workplaces, in the premises of residential, public buildings and in residential areas.’” https://files.stroyinf.ru/Data1/5/5212/index.htm (accessed May 17, 2022).

[100] “sanitary rules SanPiN 2.6.1.2523-09 "Radiation safety standards (NRB-99/2009),” Jul. 07, 2009. https://docs.cntd.ru/document/902170553 (accessed May 18, 2022).

[101] “GOST 12.1.038-82 Occupational safety standards system (SSBT). Electrical safety. Maximum allowable values of touch voltages and currents (with Amendment No. 1) dated July 30, 1982 - docs.cntd.ru.” https://docs.cntd.ru/document/5200313 (accessed May 17, 2022).

[102] “lighting requirements. VII. Requirements for natural and artificial lighting.” https://starer.ru/en/requirements-for-lighting-vii/ (accessed May 17, 2022).

[103] "SanPiN of 28.06.2012 # 82Sanitary norms and rules "Requirements for natural, artificial and combined lighting of premises of residential and public building." https://www.russiangost.com/p-366314-sanpin-of-28062012-82.aspx (accessed May 17, 2022).

[104] U. Epa and R. Protection Division, "Guide for Radiological Laboratories for the Control of Radioactive Contamination and Radiation Exposure," 2012, Accessed: May 18, 2022. [Online]. Available: www.epa.gov/narel

[105] "Russian federation federal law on radiation safety of the population," Jun. 11, 2021. https://docs.cntd.ru/document/9015351#64U0IK (accessed May 18, 2022).

[106] "Federal Law No. 181-FZ of July 17, 1999." https://mintrud.gov.ru/docs/laws/57 (accessed May 18, 2022).

[107] "GOST 12.1.038-82 Occupational safety standards system (SSBT). Electrical safety. Maximum allowable values of touch voltages and currents (with Amendment No. 1) dated July 30, 1982 - docs.cntd.ru." https://docs.cntd.ru/document/5200313 (accessed May 16, 2022).

[108] "FEDERAL RULES AND REGULATIONS IN THE AREA OF ATOMIC ENERGY USE 'GENERAL PROVISIONS FOR NUCLEAR POWER PLANT SAFETY ASSURANCE' (NP-001-15)." https://docs.secnrs.ru/documents/nps/%D0%9D%D0%9F-001-15/%D0%9D%D0%9F-001-15e.html (accessed Apr. 15, 2022).

[109] "Order of the Government of the Russian Federation 'About Approval of Rules of Fire Prevention Regime in the Russian Federation.'" https://cis-legislation.com/document.fwx?rgn=127666 (accessed Apr. 15, 2022).