Available online on 15.08.2025 at <http://jddtonline.info>

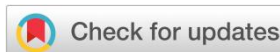
Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Research Article

Microdosimetry assessment of the radiochemical element ^{177}Lu in the treatment of metastatic prostate cancer of the LNCaP cell line

Marie Rosine Atsain-Allangba ¹, Guy Müller Okra ^{2,3}, Placide Koffi Allangba ^{3,4,5*}

¹ Laboratory of substance Natural bio-organic Chemistry, University Nangui Abrogoua, Abidjan, Côte d'Ivoire.

² Physics Teaching Unit, Laboratory of Environmental Sciences and Technologies, University Jean Lorougnon Guédé, Daloa, Côte d'Ivoire.

³ Laboratory of Fundamental and Applied Physics (LFAP), University Nangui Abrogoua, Abidjan, Côte d'Ivoire

⁴ Institute of Nuclear Medicine of Abidjan (IMENA), Biosecurity and Biosafety Pole, Medical Physics and Radiation Protection Unit, Abidjan, Côte d'Ivoire.

⁵ Department of Medical Physics, University Trieste and International Centre for Theoretical Physics (ICTP), Trieste, Italy.

Article Info:

Abstract



Article History:

Received 19 May 2025
Reviewed 26 June 2025
Accepted 18 July 2025
Published 15 August 2025

Cite this article as:

Atsain-Allangba MR, Okra GM, Allangba PK, Microdosimetry assessment of the radiochemical element ^{177}Lu in the treatment of metastatic prostate cancer of the LNCaP cell line, Journal of Drug Delivery and Therapeutics. 2025; 15(8):21-26
DOI: <http://dx.doi.org/10.22270/jddt.v15i8.7292>

*For Correspondence:

Placide Koffi Allangba, Laboratory of Fundamental and Applied Physics (LFAP), University Nangui Abrogoua, Abidjan, Côte d'Ivoire

Objective: The aim of our study is to optimize the dose to develop a new treatment protocol for prostate cancer with ^{177}Lu in order to reduce the irradiation of surrounding organs at risk.

Methods: A cell line, LNCaP, was used as a target for ^{177}Lu irradiation at the cellular level. A simple linear quadratic model implemented in the MIRDcell software was chosen to describe the survival probability of cancer cells.

Results: Our model was established with an activity range per cell of 0.01 to 0.62 Bq/cell corresponding to an absorbed dose of 2 to 125 Gy respectively. However, 0.3 Bq/cell approximately 62 Gy seemed to be the most acceptable planning as it corresponds to 7.4 GBq/cycle, the typical value delivered at 100% of tumor cell coverage. Indeed, a cellular energy distribution yields a self-dose of $S(N \leftarrow N) = 1.35\text{E-}03 \text{ Gy/Bq}\cdot\text{s}$, indicating that the nucleus absorbs more energy. Cellular absorption is much lower than that of the nucleus, with $S(C \leftarrow C) = 1.68\text{E-}04 \text{ Gy/Bq}\cdot\text{s}$. A portion of the energy is deposited in the cytoplasm, and energy is transferred between the cytoplasm and the nucleus, with $S(N \leftarrow \text{Cy}) = S(\text{Cy} \leftarrow N) = 1.30\text{E-}04 \text{ Gy/Bq}\cdot\text{s}$. The membrane cell contributes less to the cellular dose, with $S(N \leftarrow \text{CS}) = 1.30\text{E-}04 \text{ Gy/Bq}\cdot\text{s}$.

Conclusion: This study shows the necessity of a personalized pre-treatment dosimetry to deliver an optimal lethal dose to tumor cells.

Keywords: LNCaP cell line, ^{177}Lu , linear quadratic, MIRDcell

INTRODUCTION

During the 20th century, targeted radionuclide therapy became an interesting approach. A tumour treatment tool, radionuclide (TR) therapy is a treatment that uses radiopharmaceuticals (RP) to target and irradiate cancer cells. The products (RP) contain a targeting molecule (e.g., peptide or antibody) bound to a radionuclide suitable for a chelating agent; the targeting molecule binds to a receptor tumor characterized by the principle of lock and key. RT is based on the concept of administering ionizing radiation to pathological sites (usually disseminated metastasis that cannot be treated by external radiotherapy) in such a way as to cause minimal toxicity to surrounding normal tissues. Several advantages of this approach, namely its selectivity in the radiation of the target relative to less serious and infrequent side effects, and the ability to assess tumor

absorption prior to therapy using nuclear medicine imaging technique¹. The success of this treatment modality faces many challenges, including the selection and availability of radionuclides with appropriate half-lives, emission characteristic and availability of a targeting vector capable of incorporating optimal radiation, level of activity clade with a favourable pharmaceutical². The tumor response depends on the tumor absorbed by the dose and tumor radiosensitivity. Some of the radioisotopes in the lanthanide series, such as Terbium and Lutetium, reveal nuclear-appropriate half-lives although terbium is known as a powerful tool for both therapy and diagnosis, Current research has shown that radiochemical element lutetium 177 (^{177}Lu) is used in hospitals to treat neuroendocrine tumors³. This radioisotope is a hope for the treatment of prostate cancer, responsible for 90,000 deaths in Europe¹. In black

Africa, the increasing incidence of prostatic adenocarcinoma raises the problem of its characterization at the epidemiological, clinical and therapeutic levels. It occurs in relatively young patients with pejorative histoprognostic characteristics². Prostate cancer is the first male cancer in Côte d'Ivoire with 2,757 new cases whose average age is 63 years. GLOBOCAN estimated 80% metastatic cases and 1,600 deaths in 2020 and the mortality rate is estimated at 29.5 per 100,000 men³. The most developed clinical areas around lutetium 177 initially concerned neuroendocrine tumors overexpressing somatostatin receptors. Secondary prostate lesions expressing prostate specific membrane antigen (PSMA) represent a potentially considerable new field of application. This work proposes an approach based on the dosimetric evaluation of this radiochemical element, both emitter γ and β which is of medical interest for theragnostic applications for diagnostic and therapeutic purposes^{7,8}. It consists in using a pair of radioisotopes of the same element one serving the therapeutic agent and the other for the diagnosis which predict before the treatment, the biodistribution of the therapeutic radionuclide. Knowledge of biodistribution makes it possible to estimate the dose received by the patient. In addition, treatment can be monitored when a single isotope emits both therapeutic particles and photons for imaging. The aim of this work is to evaluate radiobiological effect to establish S value of ¹⁷⁷Lu to the nucleus.

MATERIALS AND METHODS

Computing Station

This work was carried out by the MIRDcell software^{4,5,6} installed on the Windows operating system of the Intel(R) Core (TM) i5-6300U CPU @ 2.40GHz, 8 GB of RAM, 500 GB of hard disk. Structural and morphological cell line data from metastatic prostate cancer were used by MIRDcell parameterization.

Biological model and software setup

Dosimetric planning was performed to optimize prostate cancer therapy treated with ¹⁷⁷Lu. A carcinogenic cell line

called LNCaP (Lymph Node carcinoma of the prostate) was selected as part of our study^{12,13}. LNCaP cells internalize the ¹⁷⁷Lu-labeled compound upon binding to PSMA¹⁴. In our method, the simple linear quadratic parameters were used. LNCaP was characterized by $\alpha = 1.081 \text{ Gy}^{-1}$ and $\beta = 0 \text{ Gy}^{-2}$. The α parameter represents the dose fraction that can cause lethal damage to a cell in a single collision by a particle. While β represents multiple collisions and is related to damage repairable by the cell itself. A more realistic approach was used in which terbium 161 activity is distributed in the nucleus (n), cytoplasm (cy) and cell surface (cs) with a repartition of 6%, 78% and 16% respectively¹⁵. In this study the whole cell was taken as source and target. In MIRDcell models, the distribution of radiopharmaceuticals into different cell regions or into the whole cell, estimates the mean activity per cell, absorbed dose and predicts the surviving fraction of labelled and unlabelled cell populations. The modelling steps are as follows, define the radioactive source, the source and target cell, the radiobiological parameters and the geometric model of the cells. In this work, the radius of the cell and its nucleus was fixed at 10 μm and 4 μm respectively and it was assumed that the radioactivity is uniformly distributed within the source region and that the distance between the centres of neighbouring cells is 20 μm (cells touching each other). To estimate survival, it was considered a 3D multicellular cluster with a radius of 150 μm , containing 1791 cells and it was assumed that different percentages of the cells were labelled with radioactivity, specifically 1%, 10% and 100%. The program causally selects the labelled cells in the cluster. The surviving fraction is calculated using the Monte Carlo method described by Howell et al.¹⁶.

RESULTS AND DISCUSSION

RESULTS

Data collection of the scenarios de simulation

Table 1 below represents the evaluation of the activity per cell of the absorbed dose and of the percentage of labelled cells according to the simulation scenarios

Table 1: Dosimetry metric values of fifteen simulation scenarios

Simulation scenarios number	1	2	3	4	5	6	7	8	9
Activity(Bq/cell)	0.62	0.62	0.62	0.31	0.31	0.31	0.1	0.1	0.1
absorbed dose (Gy)	124	125	125	64	62.7	62.4	19.5	20	20.1
Pourcentage of cells laballed(%)	1%	10%	100%	1%	10%	100%	1%	10%	100%
10	11	12	13	14	15				
0.02	0.02	0.02	0.01	0.01	0.01				
4.02	4	4.02	2.08	2.01	2.01				
1%	10%	100%	1%	10%	100%				

Activity distribution model

Different types of activity distribution were considered in the simulation between ^{177}Lu source with LNCaP whole cells as target and its continuents. The study template is shown in Figure 1.

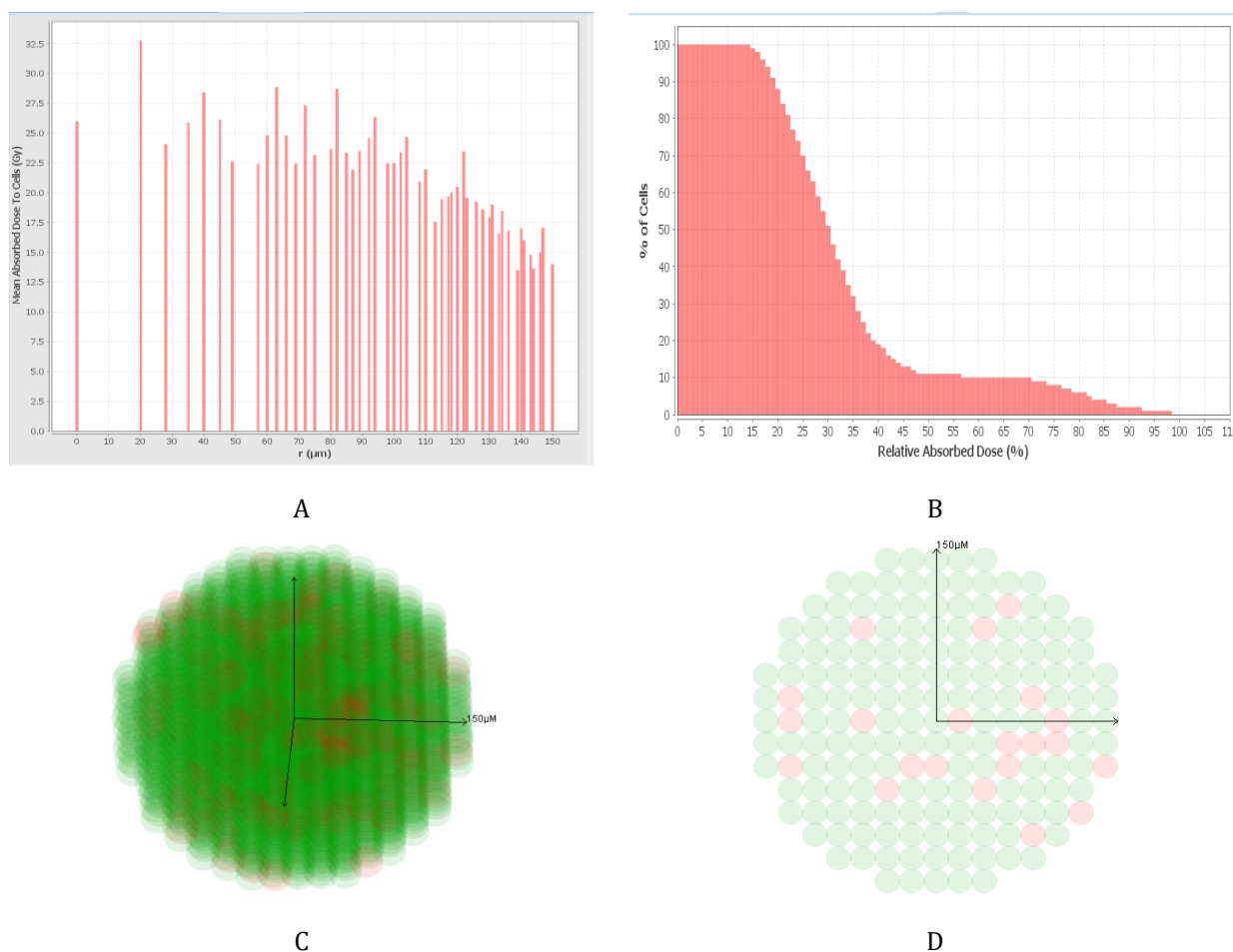


Figure 1: Planning simulation 8 with the dosimetric data 0.1 Bq/cell labelled 179 cells (10%) with 20 Gy, A: Mean Absorbed dose to cell (Gy) vs cluster radius (μm), B: % of cells vs relative absorbed dose (%), C: labelled and unlabelled cell in 3D, D: labelled and unlabelled cell in 2D

Self-S value

The table 2 represents S-values (dose conversion factors), which describe the absorbed dose per unit of activity for different cellular compartments in MIRDcell simulations.

Table 2 : S-value calculation

Distance	S(C $\leftarrow$ --C)	S(C $\leftarrow$ --CS)	S(N $\leftarrow$ --N)	S(N $\leftarrow$ --Cy)	S(N $\leftarrow$ --CS)	S(Cy $\leftarrow$ --N)	S(Cy $\leftarrow$ --CS)	S(Cy $\leftarrow$ --Cy)
μm	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s	Gy/Bq-s
Self-S	1.68E-04	1.07E-04	1.35E-03	1.30E-04	6.21E-05	1.30E-04	1.10E-04	1.68E-04

Distance (μm): The spatial distance over which dose deposition is calculated.

S(C $\leftarrow$ --C) (Gy/Bq-s): Dose absorbed by the cell (C) from a source in the cell (C) (self-dose).

Cy: cytoplasm, N: nucleus, CS: cell surface

DISCUSSION

Cellular Microdosimetry: Self-dose

Regarding Table 2, Self-dose (S(N $\leftarrow$ --N) and S(C $\leftarrow$ --C)) is the highest. The highest S-value is S(N $\leftarrow$ --N) = 1.35E-03 Gy/Bq-s, meaning the nucleus absorbs more energy when the source is inside the nucleus. The cytoplasm's

self-dose S(C $\leftarrow$ --C) = 1.68E-04 Gy/Bq-s is lower than that of the nucleus, indicating that nuclear localization of the radionuclide delivers more lethal radiation to the DNA. Also, Self-dose from nucleus to cytoplasm (S(Cy $\leftarrow$ --N)) is significant S(Cy $\leftarrow$ --N) = 1.30E-04 Gy/Bq-s, meaning that if radioactivity is localized in the nucleus, a significant portion of the energy is still deposited in the cytoplasm.

However, the reverse effect ($S(N \leftarrow Cy) = 1.30E-04$ Gy/Bq-s) is also present, suggesting mutual energy transfer between compartments. At the end, regarding, the lower dose deposition from the cell surface (CS), $S(N \leftarrow CS) = 6.21E-05$ Gy/Bq-s is the lowest value, indicating that radioactivity at the cell membrane contributes less to nuclear dose. This suggests that membrane-bound radiopharmaceuticals may have reduced direct DNA damage, relying instead on indirect effects like oxidative stress. The S values of our work are above those published for ^{177}Lu from Goddu *et al.*, having approximately similar cellular characteristics⁷. Therefore, Biological implications for ^{177}Lu Therapy is like this way, if it accumulates in the nucleus, it delivers higher radiation doses to the DNA, making it more cytotoxic. The cytoplasmic ^{177}Lu still contributes significantly to nuclear damage but is less efficient than nuclear-localized radioactivity. The effective of ^{177}Lu showed in the works of Maria Anthi Kouri *et al.* These results reveal that the combination of ^{177}Lu with gold nanoparticles significantly increases cell death and apoptosis in the liver cancer cell line¹⁸. The membrane-bound ^{177}Lu results in the lowest direct DNA damage,

meaning therapeutic efficiency may depend more on bystander effects or secondary damage mechanisms.

Impact of radiation on DNA

Clinical Considerations, for maximum therapeutic efficacy, radiopharmaceuticals should ideally target the nucleus to maximize DNA damage. If ^{177}Lu localizes in the cytoplasm, it can still be effective, but a higher administered activity may be needed. Membrane-bound ^{177}Lu therapies may require combination treatments, such as radiosensitizers or adjunct chemotherapy, to improve effectiveness. The dose-dependent increase in DNA double-strand breaks, correlating with the dose absorbed by the blood, has highlighted the kinetics of repair of radiation-induced foci over time⁸. It highlighted that β -emitters like ^{177}Lu primarily induce single-strand breaks (SSBs), but with increasing doses, double-strand breaks (DSBs) occur, leading to cell death²⁰. The importance of DNA damage in therapeutic effectiveness and the need for precise dosimetry is one of the ways to optimize treatment outcomes¹⁹.

Surviving fraction

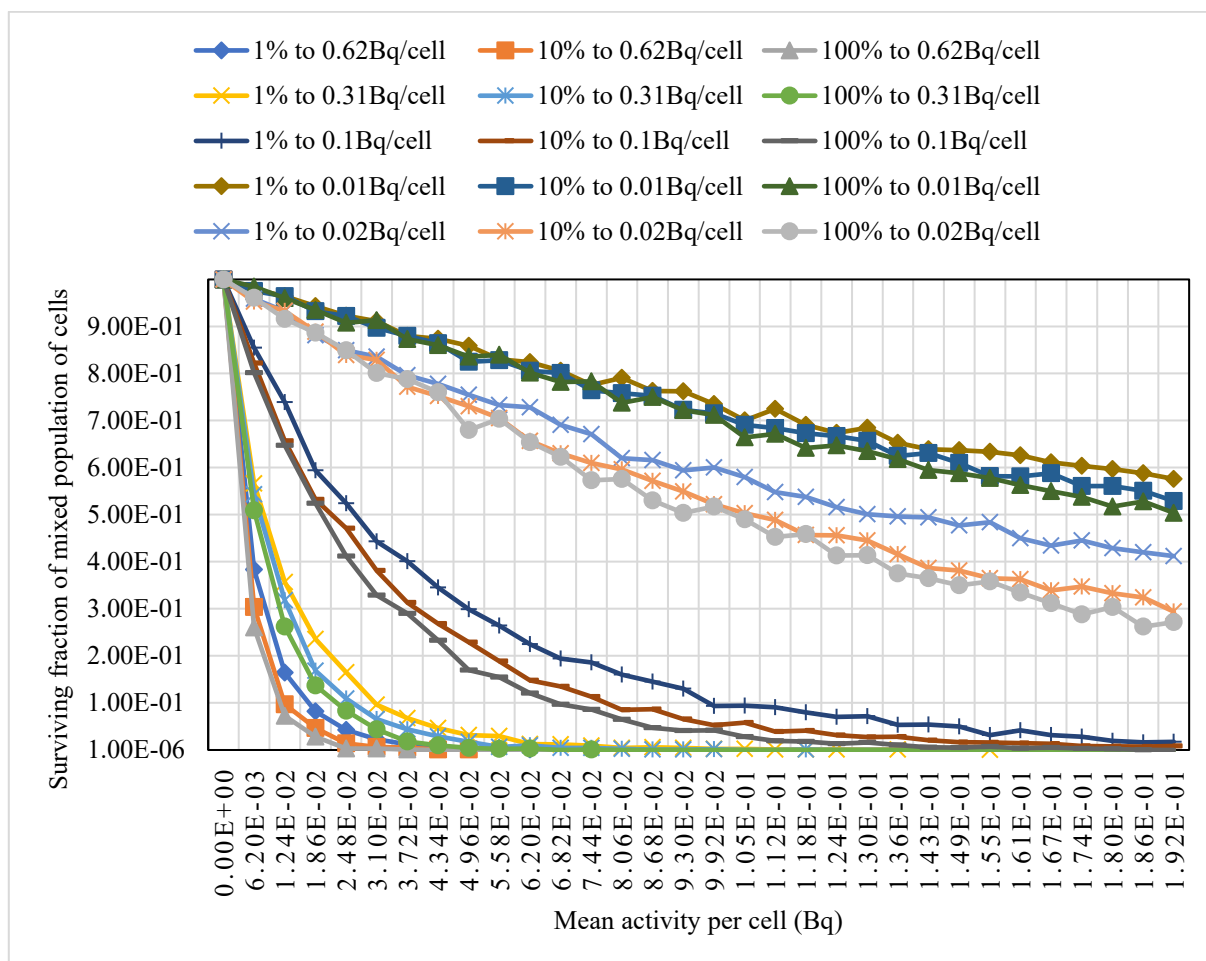


Figure 2: Surviving fraction of cells vs mean activity per cell

Fifteen simulation scenarios were conducted in this study. This plot appears to show cell survival fractions under different conditions of radioactivity per cell (Bq/cell) and percentage of labelled cells (1%, 10%,

100%). It has been observed in figure 2 that higher activity per cell leads to greater cell killing. Curves corresponding to higher activities per cell about 0.62 Bq/cell, while the absorbed dose reaches 125 Gy, decline

faster, meaning higher radiation doses lead to greater cell death. Recently, we reported iPD-L1 as a novel inhibitor peptide that specifically targets the cancer cell ligand PD-L1 (programmed death ligand 1) in immunotherapy for the treatment of breast and lung cancer. After treatment with ^{177}Lu -iPD-L1 using 0.4 Bq/cell, flow cytometry results showed a significant decrease in cell viability of 4T1 cells (dead 56.2%) compared to $^{177}\text{LuCl}_3$ (dead 34.2%) and untreated cells (dead 9.4%) ²¹. Highest Activity per cell used in our work is slightly higher than that ^{177}Lu -iPD-L1. Typically, 7.4 GBq/cycle is request for PSMA + tumors, aligning with 100% labelling optimization for prostate cancer treatment ^{22,23}. This corresponds to 0.25 Bq/cell according to our model that contains 1791 cells.

Lower % labelled cells (solid markers) show the fastest drop in survival, as every cell receives radiation directly. 1% labelled cells (lines with crosses) exhibit a much slower decline, showing that when only a small percentage of cells uptake the radiopharmaceutical, the overall survival fraction remains higher. 10% labelled cells (dashed lines) lie between the two, demonstrating an intermediate effect. Also, considering the crossfire effect, even when only 1% of cells are labelled, survival is affected. This suggests that cross-irradiation (radiation from labelled to unlabelled cells) contributes to cell killing. The crossfire effect enables the eradication of cells that are not necessarily but are affected by the radiation ²⁴ due to their larger range about 0.6 mm for ^{177}Lu beta emitters benefit from crossfire irradiation as the clustering size increase making beta particles more effective in larger cluster compared to alpha particles ^{25,26}. The effect is more pronounced at higher activity levels as shown in our work where 0.62 Bq/cell with 1% labelling still results in significant cell death. At 0.1 and 0.3 Bq/cell, drop about 20 to 62 Gy respectively. Low activity results in resistance, at 0.01 and 0.02 Bq/cell, the values are even lower about 4 Gy and 2 Gy, respectively, the survival fraction remains higher, even for 100% labelled cells. This suggests that at very low activities, the radiation dose is insufficient to induce a meaningful therapeutic effect. From a biological and clinical point of view, for effective therapy, a combination of high activity per cell and a high percentage of tagging is required. If only a small fraction of the tumour cells occupies the radiopharmaceutical, higher activity per cell is required to ensure therapeutic efficacy by crossfire radiation. Too low an activity like 0.01 Bq/cell, is unlikely to be effective even with 100% uptake. However, 0.3 Bq/cell approximately 62 Gy seemed to be the most acceptable planning. Strategies to improve absorption in all tumour cells or increase crossover can improve treatment outcomes.

CONCLUSION

At the end of our study, the results show a correlation between cellular activity and the absorbed dose. The cell survival rate decreases with increasing cellular activity, indicating a correlation between treatment efficacy and the absorbed dose. Our study highlights several key points including the efficacy of ^{177}Lu . It offers a good balance between therapy and imaging due to its γ

emission. S-values are important metrics for assessing cell dose distribution. Also, there is the importance of cellular distribution characterized by self-dose and cross-dose which emphasizes the localization of the isotope in the nucleus, cytoplasm, and cell membrane. This distribution plays a crucial role in dose absorption. This study shows the importance of Pre-Therapeutic Dosimetry that is a good tool for estimating biodistribution before treatment could help optimize protocols and improve the benefit-risk ratio.

Funding Source: No funding has been made available for this research.

Acknowledgments: The study was performed by the Medical Physics research unit, University Nangui Abrogoua in Cote d'Ivoire, ICTP, Italy. The authors acknowledge with gratitude the support from the unit.

Conflict of Interest: The author declares that there is no conflict of interest.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethics approval and consent to participants: Not applicable

REFERENCES

- Erra B, Pradere B. Place de la médecine nucléaire au sein de la prise en charge du cancer de la prostate Nuclear medicine for prostate cancer management. *Progrès en urologie* 2019;29:S2-S7 [https://doi.org/10.1016/S1166-7087\(19\)30165-4](https://doi.org/10.1016/S1166-7087(19)30165-4) PMID:31307627
- Umbricht CA, Benešová M, Schmid RM, et al. 44Sc-PSMA-617 for radiotheragnostics in tandem with ^{177}Lu -PSMA-617-preclinical investigations in comparison with 68Ga-PSMA-11 and 68Ga-PSMA-617. *EJNMMI Res.* 2017; 7:9. <https://doi.org/10.1186/s13550-017-0257-4> PMID:28102507 PMCID:PMC5247395
- Umbricht CA, Koster U, Bernhardt P, et al. Alpha-PET for Prostate Cancer: Preclinical investigation using ^{149}Tb -PSMA-617. *Sci Rep.* 2019 ;9:17800. <https://doi.org/10.1038/s41598-019-54150-w> PMID:31780798 PMCID:PMC6882876
- La lutte contre le cancer intensifiée grâce au SCK CEN et à l'IRE. <https://www.ire.eu/public/media-room/la-lutte-contre-le-cancer-intensifiee-grace-au-sck-cen-et-a-l-ire>. Consulted the 20/06/2024
- NZAMBA Bisselou Paul Ludovic, ODO Bitti Addé, NZIENGUI Tirogo Christian, KOUASSI Kouamé Konan Yvon, KAGAMBEGA Zoewendbem Arsène Gaetan, TOURE Mactar. Prostate cancer in black subjects in Ivory Coast Prostate cancer in black subjects in Côte d'Ivoire. *Rev int sc méd Abj. RISM* 2021;23(1):49-54.
- National Cancer Control Program (PNLcaP) of the Ministry of Health, Public Hygiene and Universal Health Coverage of the Republic of côte d'ivoire.
- <https://www.pnlca.org/copy-of-cancer-en-cote-d-voire-2>. Consulted the 04/07/2024
- Elisa Mattar and Nicole Jawerth. Office of Public Information and Communication. IAEA Bulletin. See and Kill Cancer Cells. <https://www.iaea.org/fr/newscenter/news/voir-et-tuer-les-cellules-cancereuses>. Consulted the 04/07/2024

9. Jabbari M and Pandesh S. Monte carlo investigation of S values for ¹¹¹In radionuclide therapy. *Braz. J. Rad. Sci.* 11-04(2023) 01-12, e2348. <https://doi.org/10.15392/2319-0612.2023.2348>
10. Vaziri B, Wu H, Dhawan AP, Du P, Howell RW. MIRD Pamphlet No. 25: MIRDcell V2.0 Software Tool for Dosimetric Analysis of Biologic Response of Multicellular Populations. *J Nucl Med.* 2014 Sep;55(9):1557-64. <https://doi.org/10.2967/jnumed.113.131037> PMID:25012457
11. Katugampola S, Wang J, Rosen A, et al. MIRD Pamphlet No. 27: MIRDcell V3, a revised software tool for multicellular dosimetry and bioeffect modeling. *J Nucl Med.* 2022;63:1441-1449. <https://doi.org/10.2967/jnumed.121.263253> PMID:35145016 PMCID:PMC9454469
12. Katugampola S, Wang J, Howell RW. MIRD Pamphlet No. 30: MIRDcell V4, Artificial intelligence tools to formulate optimized radiopharmaceutical cocktails for therapy. *J Nucl Med.* submitted.
13. Chan HS, de Blois E, Morgenstern A, Bruchertseifer F, de Jong M, Breeman W, et al. In Vitro comparison of ²¹³Bi- and ¹⁷⁷Lu-radiation for peptide receptor radionuclide therapy. *PLoS ONE* 2017;12(7):e0181473. <https://doi.org/10.1371/journal.pone.0181473> PMID:28732021 PMCID:PMC5521788
14. Loubeau G. Impact of nucleophosmin protein (NPM1) overexpression on prostate cancer progression. *Agricultural Sciences. University Blaise Pascal - Clermont-Ferrand II*, 2012. France. fNNT : 2012CLF22319ff. fftel-00870415f
15. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with ¹⁷⁷Lu-labelled PSMA-ligands (¹⁷⁷Lu-PSMA RLT). *Eur J Nucl Med Mol Imaging.* 2019 46:2536-44. <https://doi.org/10.1007/s00259-019-04485-3> PMID:31440799
16. Borgna F et al. "Combination of terbium-161 with somatostatin receptor antagonists-a potential paradigm shift for the treatment of neuroendocrine neoplasms". In: *European journal of nuclear medicine and molecular imaging* 2021;1-14. <https://doi.org/10.1007/s00259-021-05564-0> PMID:34625828 PMCID:PMC8921065
17. Howell RW, Rajon D, Bolch WE. Monte Carlo simulation of irradiation and killing in three-dimensional cell populations with lognormal cellular uptake of radioactivity. *Int J Radiat Biol.* 2012; 88:115-122. <https://doi.org/10.3109/09553002.2011.602379> PMID:21745001 PMCID:PMC4029158
18. Goddu SM, Howell RW, Rao DV. Cellular dosimetry: absorbed fractions for monoenergetic electron and alpha particle sources and S-values for radionuclides uniformly distributed in different cell compartments. *J Nucl Med.* 1994; 35:303-316.
19. Maria Anthi Kouri, Anastasios Georgopoulos , George E Manios , Eirini Maratou , Aris Spathis , Sofia Chatziioannou , Kalliopi Platoni , Efstathios P Efstathopoulos. Preliminary Study on Lutetium-177 and Gold Nanoparticles: Apoptosis and Radiation Enhancement in Hepatic Cancer Cell Line. *Curr Issues Mol Biol.* 2024 Oct 30;46(11):12244-12259. <https://doi.org/10.3390/cimb46110727> PMID:39590321 PMCID:PMC11592690
20. Eberlein U, Nowak C, Bluemel C, Buck AK, Werner RA, Scherthan H, Lassmann M, DNA damage in blood lymphocytes in patients after (¹⁷⁷)Lu peptide receptor radionuclide therapy. *Eur J Nucl Med Mol Imaging.* 2015 Oct;42(11):1739-1749. <https://doi.org/10.1007/s00259-015-3083-9> PMID:26048612 PMCID:PMC4554740
21. . Monfared YK, Heidari P, Klempner SJ, Mahmood U, Parikh AR, Hong TS, Strickland MR, Esfahani SA, DNA Damage by Radiopharmaceuticals and Mechanisms of Cellular Repair. *Pharmaceutics.* 2023 Dec 12;15(12):2761. <https://doi.org/10.3390/pharmaceutics15122761> PMID:38140100 PMCID:PMC10748326
22. Luna-Gutiérrez M, Azorín-Vega E, Oros-Pantoja R, Ocampo-García B, Cruz-Nova P, Jiménez-Mancilla N, Bravo-Villegas G, Santos-Cuevas C, Meléndez-Alafort L, Ferro-Flores G. Lutetium-177 labeled iPD-L1 as a novel immunomodulator for cancer-targeted radiotherapy. *EJNMMI Radiopharm Chem.* 2025 Jan 22;10(1):5. <https://doi.org/10.1186/s41181-025-00328-9> PMID:39843795 PMCID:PMC11754567
23. Murthy V, Voter AF, Nguyen K, Allen-Auerbach M, Chen L, Caputo S, Ledet E, Akerele A, Tachayi AM, Lawhn-Heath C, Wang T, Carducci MA, Pomper MG, Paller CJ, Czernin J, Solnes LB, Hope TA, Sartor O, Calais J, Gafita A. Efficacy and Toxicity of [¹⁷⁷Lu] Lu-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: Results from the U.S. Expanded-Access Program and Comparisons with Phase 3 VISION Data. *J Nucl Med* 2024; 65:1740-1744. <https://doi.org/10.2967/jnumed.124.267816> PMID:39327018
24. Sartor O, de Bono J, Chi KN. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091-1103. <https://doi.org/10.1056/NEJMoa2107322> PMID:34161051 PMCID:PMC8446332
25. Nardo GLD. Concepts in radioimmunotherapy and immunotherapy: Radioimmunotherapy from a Lym-1 perspective *Semin Oncol.* 2005 Feb; 32 (1suppl1): S27-35. <https://doi.org/10.1053/j.seminoncol.2005.01.011> PMID:15786023
26. Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges *Nat Rev Drug Discov* 2020;19:589-608 <https://doi.org/10.1038/s41573-020-0073-9> PMID:32728208 PMCID:PMC7390460
27. Tranel J, Palm S, Graves SA, Feng FY, Hope TA. Impact of radiopharmaceutical therapy (¹⁷⁷Lu, ²²⁵Ac) microdistribution in a cancer associated fibroblasts model. *EJNMMI Phys.* 2022 Sep 30;9(1):67. <https://doi.org/10.1186/s40658-022-00497-5> PMID:36178531 PMCID:PMC9525486