KDUiRC
INTERNATIONAL RESEARCH CONFERENCE

17th INTERNATIONAL RESEARCH CONFERENCE

"Unravelling the Paradigm Shift: Revolutions in the Era of AI"

26TH - 27TH SEPTEMBER 2024

ALLIED HEALTH SCIENCES

PROCEEDINGS

General Sir John Kotelawala Defence University

17th INTERNATIONAL RESEARCH CONFERENCE

UNRAVELLING THE PARADIGM SHIFT: REVOLUTIONS IN THE ERA OF AI

ALLIED HEALTH SCIENCES

General Sir John Kotelawala Defence University
Ratmalana, Sri Lanka.

KDU PRESS

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Message from the Chief Guest

I am truly honoured to welcome all the distinguished participants to the 17th International Research Conference (IRC) at General Sir John Kotelawala Defence University (KDU). This annually organized conference serves as a unique milestone showcasing the rich research culture deeply embedded within KDU. As a prestigious seat of learning, novelty and innovation remain at the heart of KDU's mission. Therefore, 'Unravelling the Paradigm Shift: Revolutions in the Era of AI' has been chosen as the key theme of IRC 2024.

Moving ahead with the momentum of modern-day research, we are set to uncover the extensive impacts of artificial intelligence, not just in defence but across every facet of national interest. Currently, AI has become a driving force, reforming our defence strategies, transforming healthcare, and restructuring our educational frameworks and infrastructure.

Investing in research is essential for national advancement, promoting innovation, formulating policies, and offering solutions that address our most pressing challenges. Hence, the IRC serves as a vital platform that fosters such great endeavours, contributing significantly to national development. Our responsibility as defenders of national security is profound, extending beyond traditional roles to include the ethical integration of advanced technologies that ensure our nation's safety and prosperity.

KDU stands as a symbol of a rich and diverse research culture across many disciplines. It is also a hub for high-quality research, upholding international standards of academic excellence. This conference represents a critical meeting of minds where leading experts converge to define strategies for our future. Each discussion and presentation at this event is a step toward securing a thriving, prosperous future for our region.

I extend my best wishes to all for a successful and productive conference, eagerly anticipating the innovative ideas and transformative insights that will undoubtedly arise.

GENERAL SHS KOTTEGODA (Retd) WWV RWP RSP VSV USP ndc
Chancellor General Sir John Kotelawala Defence University

Message from the Keynote Speaker

Brain health is a holistic concept encompassing cognitive, sensory, social-emotional, behavioural, and motor functions, enabling individuals to achieve their full potential. With one in three people globally affected by a brain disorder, the urgency for preventive brain health initiatives is evident. Since the inception of World Brain Day in 2014, there has been a renewed global focus on this critical area. The World Federation of Neurology (WFN), in collaboration with key organizations such as the American Academy of Neurology (AAN), the European Academy of Neurology (EAN), and the Asian Regional Consortium of Headaches (ARCH), has led the charge to raise awareness and promote brain health worldwide.

This keynote address will outline the journey of World Brain Day and its impact on the global brain health movement, with a specific focus on prevention. It will explore the evolution of brain health concepts and the alarming prevalence of brain disorders, emphasizing the need for urgent, coordinated action. Central to this effort is the role of artificial intelligence (AI) in enhancing preventive brain health strategies. AI-driven technologies are increasingly being used to predict, diagnose, and monitor brain health conditions, enabling earlier interventions and more personalized approaches to prevention.

The address will highlight the author's pioneering work in community-based programs, public health campaigns, and international collaborations. It will underscore the critical role of prevention, early intervention, and AI-powered tools in improving quality of life and reducing the global burden of brain disorders. The ultimate goal is to advance comprehensive brain health initiatives that leverage cutting-edge technologies to ensure a healthier future for all.

Professor Tissa Wijeratne
DR OAM MD PhD FRACP FRCP(London) FRCP (Edin) FAAN (USA) FEAN (EAN) Professor and Chair, Director, Senior Neurologist, Department of Neurology, Western Health, Victoria, Australia Co-Founder and Co-Chair, World Brain Day, World Federation of Neurology

Message from the Vice-Chancellor

Greetings to all participants, speakers, and guests of the 17th International Research Conference (IRC) at KDU. This year's IRC is centered around a timely theme that has sparked diverse dialogues in the realms of research and innovation. The theme, 'Unravelling the Paradigm Shift: Revolutions in the Era of AI', serves as an eye-opener for both eminent and novice researchers across the globe. It also highlights the critical role that advanced technologies play in shaping our world.

At KDU, we take pride in being at the forefront of defence education in Asia, a distinction affirmed by our high rankings and our pivotal role in shaping global security dialogues. KDU claims to have a unique history of providing high-quality education for both military and civilian students. It also proudly stands as a thriving hub for cutting-edge research that addresses pressing global and national issues. We strongly believe in fostering a rich and diverse research culture among KDU's students and staff, aligned with international standards. Therefore, IRC is recognszed as a key event in KDU's annual calendar, emphasizing its significance in the institution's academic and research endeavours.

This year, we aim to explore the revolutionary impacts of AI across diverse disciplines, reaffirming our commitment to leading these discussions on a global scale. The insights shared here will undoubtedly spark new research initiatives and strategic collaborations, enhancing Sri Lanka's stature as a leader in both academic and strategic domains.

I extend my sincere gratitude to all those whose collective efforts have brought this conference to a reality. Your contributions ensure that KDU plays a prominent role in the international arena, driving discussions that will shape the future of technology and strategy. I look forward to a successful event, characterized by insightful discussions and pioneering ideas.

REAR ADMIRAL HGU DAMMIKA KUMARA, VSV, USP, psc, MMaritimePol, BSc (DS)
Vice Chancellor General Sir John Kotelawala Defence University

Message from the Chairperson

It is my honour, as the Chairperson, to welcome you all to the 17th International Research Conference at KDU. This year, we explore how artificial intelligence has evolved from a technological innovation into a catalyst for transformative change across numerous sectors. With an impressive selection of 441 research papers, drawn from nearly 1000 submissions, our conference spans across 11 distinct tracks covering a wide range of disciplines. Our theme, "Unravelling the Paradigm Shift: Revolutions in the Era of AI," highlights the profound and far-reaching transformations that AI is driving—from reshaping urban infrastructure to revolutionizing healthcare. The conference is designed to promote interdisciplinary dialogue, addressing not only technological advancements but also the ethical, social, and economic implications of these developments. One of our key objectives is to create a platform where researchers, professionals, and thought leaders can come together, exchange ideas, and foster collaborative initiatives that will push the boundaries of innovation. I am deeply grateful to all our keynote speaker and the plenary speakers, other presenters, , participants, and the entire organizing team for their tireless efforts and contributions. Your dedication to advancing knowledge is what brings this conference to life, positioning it as a critical forum in global research. Together, we are charting a path toward a future where technology and society grow hand in hand, reshaping the landscape of not just research but our daily lives. Let's engage in meaningful discussions that will inspire new perspectives and drive impactful solutions. Here's to a successful conference, rich in insight and collaboration. Finally, I would like to extend my best wishes to all the presenters, authors, and participants joining the KDU IRC 2024, whether on-site or online. I hope each of you finds this conference not only informative and enjoyable but also an encouraging opportunity to experience the warm hospitality of KDU throughout these two fruitful days.

Dr. Nirosha Wedasinghe
Ph.D(KDU-SL), MIT(CStud-Aus),B.Sc in Comp IS (London Met -UK), SMIEEE(US), MBSC(UK), MCS(SL), FISDS(Japan) Senior Lecturer cum Director -Centre for Gender Equity and Equality General Sir John Kotelawala Defence University Conference Chair-IRC 2024

Message from the Secretary

As we gather for the 17th International Research Conference at KDU, I extend a warm and heartfelt welcome to all participants, researchers, and thought leaders. This year, we proudly present 441 research papers selected from nearly 1,000 submissions, spanning across 11 tracks in diverse fields such as Defence and Strategic Studies, Medicine, Health Sciences, Engineering, Technology and Computing, Basic sciences, Law, Social Sciences and Humanities, and the Built Environment and Spatial Sciences. Our theme, "Unravelling the Paradigm Shift: Revolutions in the Era of AI," reflects the profound ways that AI is transforming our world, becoming integral to our lives and work. The discussions here aim to explore how AI can address global challenges, drive innovation, and foster interdisciplinary collaborations that will shape the future. Looking ahead, the future of IRC lies in broadening its horizons. We aim to increase international participation, diversify the scope of research, and establish global research consortia to tackle real-world problems that extend beyond the borders of Sri Lanka. The insights gained here must lead to actionable outcomes, particularly in formulating policy recommendations in areas such as AI in defence, public health, and education. This conference is more than just a forum for discussion; it is a platform where the brightest minds collaborate to drive change. I extend my heartfelt thanks to all our speakers and participants for their dedication and contributions. Together, we are not only shaping the future of research but also crafting solutions that will impact society on a global scale. Here's to a successful and inspiring conference that drives innovation, shapes policy, and sparks meaningful collaboration.

Dr. HM Prasanna Herath
Ph.D. (USJ), RN(SLNC), B.Sc(Nursing) Hons (UPSL), CTHE Senior Lecturer Faculty of Allied Health Sciences Erasmus coordinator General Sir John Kotelawala Defence University Conference Secretary- IRC 2024

Message from the Dean

It is with great pleasure and honour that I extend a warm welcome to all participants of the International Research Conference of KDU 2024. As the Dean of the Faculty of Allied Health Sciences, I am thrilled to be part of this remarkable gathering of scholars, researchers, and practitioners dedicated to advancing knowledge and innovation in our field. This conference provides an invaluable platform for exchanging ideas, fostering collaborations, and exploring new frontiers in Allied Health Sciences in the era of AI. It is through such collaborative efforts that we can address the pressing challenges of our time and improve health outcomes on a global scale. I am confident that the diverse range of presentations, discussions, and workshops planned for this year's conference will stimulate insightful dialogue and contribute significantly to our collective understanding. I encourage all participants to engage actively, share your perspectives, and take full advantage of this opportunity to learn from one another. I extend my deepest gratitude to the organizing committee, keynote speakers, and all contributors who have worked diligently to make this event a success. Your commitment and enthusiasm are truly inspiring. May this conference be a memorable and impactful experience for all, and may it empower the future developments in health sciences in this era of AI.

Dr Ranga Perera
MBBS, MS, FRCS (Eng), FRCS (Ed.) FCSSL Dean Faculty of Allied Health Sciences Consultant Oncological Surgeon Surgeon Captain Sri Lanka Navy Senior Lecturer in Surgery General Sir John Kotelawala Defence University

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CONFERENCE PROCEEDINGS

Evaluation of the Level of Knowledge and Awareness of Radiation Protection among Radiation Therapists in Sri Lanka

MRM Anaas[1#], WWT Nethmini[1], HKA Dharmasiri[1], and R Tudugala[1]

[1]*Department of Radiography & Radiotherapy, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Sri Lanka*

[#] anaasdxd123@gmail.com

Abstract *— Radiation therapists are exposed to ionizing radiation during treatments making it essential for them to understand and apply radiation protection principles to safeguard their health. Inadequate training or knowledge can lead to unsafe practices and increased exposure risks. This study aims to assess knowledge and awareness on radiation protection among radiation therapists in Sri Lanka, identify existing knowledge gaps, and guide targeted training to enhance safety protocols and improve care quality. A descriptive cross-sectional study was conducted to analyze characteristics and factors associated with radiation therapists. Data were summarized by frequency and in terms of mean and standard deviation, and normality was assessed using the Kolmogorov-Smirnov test. Non-parametric tests, namely Spearman's correlation and Kruskal-Wallis H-test were used for statistical analysis since the data did not follow normal distribution. The criterion for statistical significance was set at a p-value less than 0.05. The study included a sample size of 91, from which 52 responses were successfully collected. The Kruskal-Wallis test showed significant differences in general radiation protection knowledge (p = 0.03) and the total score of knowledge and awareness of radiation protection based on educational qualifications (p =0.05). However, no significant differences were found in the mean rank scores of radiation protection knowledge related to working experience (p > 0.05). This study verified that the overall score of knowledge and awareness on radiation protection among radiation therapists in Sri Lanka was quite satisfactory.*

Keywords *— radiation therapists, radiation protection, safety practices, treatment doses*

I. INTRODUCTION

A. Background

Radiation contains charged and uncharged particles along with gamma radiation and X-rays. Natural sources and man-made or artificial sources are the sources of this radiation. These radiations are ionizing, immoderate exposure of the human body to those radiations causes harmful effects (Tanha et al., 2019). Ionizing radiations are prominent to create mutations and chromosomal aberrations in males, females, and foetuses when the threshold limit is overreached. Some adverse effects appear immediately after exposure while others may not show themselves until many years later (Fiagbedzi *et al.*, 2022). Justification, optimization (As Low As Reasonably Achievable (ALARA)), and dose optimization are the three principles of radiation protection. It also has rules which can be divided into three classes namely distance, exposure time, and shielding for external irradiation (Fiagbedzi *et al.*, 2022). Radiation therapists (RTs) administer radiation treatments but are at risk of exposure to harmful ionizing radiation. To protect their health and minimize risks, they must understand and apply radiation protection principles. However, insufficient training or knowledge in radiation protection can lead to unsafe practices and higher radiation exposure, which endangers both therapists and patients.

B. History of radiotherapy service in Sri Lanka.

1. National Cancer Institute Maharagama

The Department of Radiotherapy, General Hospital, Colombo (GHC) was operational in the main X-ray department before 1952, with a set of Strontium-90 eye plaques and KX-10 Grenz X-ray machines. Sr-90 eye plaques were utilized for beta-ray treatment of conjunctivitis and inner canthus growth. The KX-10 Granz ray machine was utilized for the treatment of keloids. In 1952, the radiotherapy department was shifted to the National Cancer Institute Maharagama (NCIM), the name change from NCIM to Apeksha Hospital Maharagama (AHM) occurred somewhere in 2012/13, and the eye plaque treatment was continued at the GHC with consultant radiotherapists and therapy radiographers were visiting from NCIM until its decommissioning in 1996. The KX-10 Grenz ray machine was moved to the NCIM around 1971, and two Deep X-ray Therapy (DXRT) machines and a Superficial X-ray Radiation therapy (SXRT) machine were installed at NCIM in 1955, but all the machines were decommissioned by 1980. Radium brachytherapy and radiation protection services were established in the latter part of the 1950s. Additionally, I-131 therapy for thyroid disorders and Prosperous-32 therapy for bone disorders and diagnostic tests such as uptakes and neck scans using I-131 were carried out at the NCIM. The equipment fleet expanded to include the Theratron junior Co-60 machine (55 cm Source Surface Distance (SSD)) and three deep X-ray (DXR) machines, in addition to the KX-10. A stock of Radium 226 needles and tubes was established at the NCIM. The Radium

safe containing Radium-226 tubes and needles was established in NCIM around 1955, but they have been unused since 1975. Intra cavitary radium, surface mould, and implant treatments were started in 1956, but these treatments have not been practiced since 1975. The NCIM expanded radiation protection services in terms of photographic films, for the country's radiological centres and staff, but personal dosimetry service ceased in 1992, and it was taken over by the Atomic Energy Authority in Sri Lanka. The Cobalt teletherapy machines, Theratron Junior (55 cm SSD) and Picker (80 cm SSD) were installed in 1958 and 1976, respectively, but both were decommissioned in the 1990s. I-131 uptakes, scans, and therapy were introduced in 1968, and Prosperous-32 for bone cancer treatment was also started. The imaging of intrauterine applicators by a C-arm fluoroscopy machine and brachytherapy planning were introduced in 1986 and continued to date on a multisource brachytherapy unit. The Eldorado Cobalt Therapy machine (80 cm SSD) was installed in 1992 and was decommissioned in 2002 and was replaced by Theratron 780E model. Conventional Simulator and Ralstron brachytherapy units were decommissioned in 2000 and 2003, respectively. Varian Linear Accelerator (LA), Computed Tomography (CT) simulator, and new treatment planning system were installed in 2006 and are still functioning. Multisource brachytherapy High Dose Rate (HDR) unit (source Cobalt-60) was installed in 2007 and is still functioning. Elekta Synergy LA and Elekta compact single-energy LA units were installed in 2013 and 2022, respectively, and are functioning currently. (Ref. former SR, AHM)

2. Decentralization of Radiotherapy in Sri Lanka.

After the establishment of the NCIM, a significant stride was made in decentralizing radiotherapy departments across the country. Commencing in the early 1980s, the Kandy Hospital became a cornerstone in this effort, providing vital radiotherapy services to the central region. Subsequent years witnessed the expansion of this decentralized network with Teaching Hospital Karapitiya in 1984, Teaching Hospital, Jaffna in 1995, General Hospital, Badulla around 2000, and Teaching Hospital, Anuradhapura in 2004. The journey towards decentralization of government hospitals continued with the inauguration of the Teaching Hospital, Batticaloa. While the decentralization of government hospitals, and private institutions played a pivotal role in establishing radiotherapy services across Sri Lanka (Ref. former SR, AHM). The Ceylinco Health Care Centre entered the scene in 2007 (Tomotherapy Treatment Hospital History - Ceylinco Cancer Center Sri Lanka, 2018), followed by Asiri in 2018 (Asiri AOI Cancer Centre launched | Daily News, 2018), collectively contributing to the development of a comprehensive and widespread network of radiotherapy departments. This collaboration between public and private healthcare sectors highlights the nation's commitment to broadening access to critical medical treatments and ensuring healthcare equity across various regions.

C. History of Radiographer's education in Sri Lanka.

Between 1942 and 1946 a consultant sponsored by the World Health Organization (WHO) started training Radiographers at the School of Radiography, GHC. The original batch of radiographers was trained in both radiography and radiotherapy, and they worked in both fields. Basic X-ray and fluoroscopy machines, as well as Sr-90 eye plaques, and a KX-10 superficial X-ray therapy machine (50 KVp) were used for their training. The therapy department was established in the main X-ray department of GHC. From 1946 to 1971 two separate courses were offered for therapy and diagnostic radiographers by the School of Radiography, with training conducted under the Society of Radiographers, United Kingdom (UK). The qualified radiographers were granted the professional qualification of Member of the Society of Radiographers (MSR), UK. The entry qualifications at that time were the Bioscience and the Physical science streams of the higher school certificate (HSC) examination. Most of the applicants for the training were those who could not enter the Medical Faculty of the University of Ceylon (Sri Lanka).

In 1952, the Radiotherapy Department was moved to the NCIM, but therapy radiographers' training was continued at the School of Radiography, GHC, under the Society of Radiographers (SOR), UK. The first year of the training covered common subjects, while the second year focused on hands-on training at the diagnostic department of GHC for diagnostic radiographers and NCIM for therapy radiographers. The school taught patient care radiographic photography, diagnostic techniques, radiotherapy techniques, equipment, and instrumentations.

In 1972, the MSR qualification for radiographers was scrapped by the Department of Health due to a shortage of qualified radiographers in the country. The School of Radiography continued to offer standard training for both diagnostic and therapy radiographers, leading to local qualifications of certificates of proficiency in radiography and radiotherapy separately. The fleet of radiotherapy equipment expanded to include three Cobalt units and later four Theratron-760 C and E models. In the late 1990s and early 2000, unionists agitated for university degree programs for radiography and radiotherapy, and the professions ultimately merged under the designation of professions supplementary to medicine (PSM). The University of Peradeniya (UOP) started offering degree programs in Radiography and Radiotherapy in 2005, with Prof Badra Hewavithana and Prof Chula Gunawardena playing pioneering roles.

Since 2005, the NCIM has been the venue for clinical training for UOP radiotherapy undergraduates. The NCIM

had 4 Cobalt-60 units and other advanced equipment, such as Varian and Elekta LA machines and a CT Simulator unit. In 2016, General Sir John Kotelawala Defence University (KDU) started offering a degree program in Radiotherapy, with clinical training taking place at AHM. The diploma program for therapy radiographers was discontinued, but the diploma program for diagnostic radiography was still running (Ref. former SR, AHM).

D. Current radiotherapy services in Sri Lanka.

In the government sector, several hospitals have been identified as the main radiation oncology centres in providing radiation therapy services. AHM stands out with its comprehensive facilities, including LAs, Cobalt-60 teletherapy machines, a brachytherapy machine, a CT simulator, and a mould room, supported by a team of around 35 RTs. General Hospital Kandy, another prominent government institution, offering a similar range of resources, including LAs, Cobalt-60 teletherapy machines, a brachytherapy machine, a CT simulator, and a mould room. With around 15 RTs, this hospital serves a significant number of patients in need of radiation therapy. Teaching Hospital Karapitiya focuses on delivering radiation therapy through a LA, Cobalt-60 teletherapy machine, a CT simulator, and a mould room, supported by around 8 RTs. Teaching Hospital Jaffna, with its team of around 7 RTs, provides radiation therapy services utilizing a LA, a CT simulator, and a mould room. Teaching Hospital Batticaloa, with around 6 RTs, offers radiation therapy services through a LA, a CT simulator, and a mould room. Teaching Hospital Anuradhapura focuses on Cobalt-60 teletherapy and has around 4 RTs and their services, combined with the available mould room facilities. General Hospital Badulla, supported by around 5 RTs, specializes in Cobalt-60 teletherapy and offers mould room services. Teaching Hospital Kurunegala specializes in I-131 administration and has 2 RTs. Lastly, General Hospital Hambantota, with its 2 RTs, offers mould room facilities to support radiation therapy treatments.

In the private sector, Ceylinco Health Care Centre and Asiri Surgical Hospital are key providers of radiation therapy. Ceylinco Health Care Centre employs 3 RTs and offers a comprehensive range of equipment, including a LA, Tomotherapy unit, a brachytherapy machine, and a CT simulator. Asiri Surgical Hospital, with its 4 RTs, focuses on delivering radiation therapy through the Linac-Ture Beam system and a Positron Emission Tomography (PET) CT simulator. Altogether, there are around 91 RTs providing services in the whole country. These RTs are either diplomates passed out from the School of Radiography under the Ministry of Health or graduates passed out from the Universities of Sri Lanka.

The assessment of this research identifies gaps in radiation protection knowledge, guiding targeted training and interventions to enhance radiation safety protocols and improve overall care quality. The general objective of this study is to assess the level of radiation protection knowledge and awareness among radiation therapists in Sri Lanka. The specific objectives are to evaluate the understanding of radiotherapy treatment doses, to identify the safety practices followed by radiation therapists in relation to radiation protection, to determine the gaps in knowledge and awareness related to radiation protection, and to provide recommendations for improving the radiation protection knowledge and awareness.

II. METHODOLOGY

A descriptive cross-sectional study design was employed to investigate and analyze the characteristics and factors associated with a sample population of RTs. The research was carried out at all radiation treatment departments in Sri Lanka over a two-month period from 30th of November 2023 to 30th of January 2024. A multiple-choice questionnaire in the medium of English comprising two sections was given out to 91 participants to answer using hybrid mode (Google form and Printed papers). The second part was further categorized into three sub-sections, Section 1 consisted of ten questions related to general radiation protection, Section 2 included ten questions about safety practices performed by RTs, and Section 3 comprised seven questions pertaining to the radiotherapy treatment doses. The data obtained from RTs was analyzed by descriptive and inferential statistics to find descriptive statistics of the sample population, correlations and associations of dependent and independent parameters using the IBM Statistical Package for Social Sciences (SPSS) v26.0. The obtained data was described based on frequency and in terms of mean and standard deviation. The normality of data was checked by Kolmogorov-Smirnov test. Non-parametric tests, namely Spearman's correlation and Kruskal-Wallis H-test were used for statistical analysis since the data did not follow normal distribution. The criterion for statistical significance was set at a p-value less than 0.05.

III. RESULTS

The research employed a sample size of 91, from which 52 samples were successfully collected. Among the population, four outrightly opposed in participation in the research. Additionally, 39 individuals did not respond to the questionnaire.

Table 1. Characteristics of the study sample.

	TOTAL		TOTAL
Sex		**Highest qualification**	
Male	39 (75%)	Higher Diploma	36 (69.2%)
Female	13 (25%)	BSc	13 (25%)
		MSc	3 (5.8%)
Further education		**Working experience**	
Related to radiation therapy	15 (35.7%)	<5	11 (21.2%)
Not Related to Radiation therapy	27 (64.3%)	5-10	9 (17.3%)
		10-20	23 (44.2%)
		>20	9 (17.3%)

Table 2.

Question number	Research question	Incorrect answer	Correct answer
Section 1			
S1 Q1	What is the most common type of ionizing radiation used in radiotherapy presently?	4 (7.7%)	48 (92.3%)
S1 Q2	Which of the following is NOT a primary source of ionizing radiation in a radiation therapy department?	4 (7.7%)	48 (92.3%)
S1 Q3	What is the term used to describe the process of reducing the intensity of a radiation beam as it passes through a material.	7 (13.5%)	45 (86.5%)
S1 Q4	What is the purpose of using beam modifiers, such as wedges or shielding blocks, in radiotherapy?	11 (21.2%)	41 (78.8%)
S1 Q5	What is the potential long-term effect of radiation exposure to RTs?	11 (21.6%)	40 (78.4%)
S1 Q6	What is the unit of measurement for the amount of radiation absorbed by a material, such as human tissue?	20 (38.5%)	32 (61.5%)
S1 Q7	What is the concept of "ALARA" in radiation protection?	0 (0.0%)	51 (100.0%)
S1 Q8	Which of the following factors can affect the depth of radiation penetration in tissue during radiotherapy?	29 (55.8%)	23 (44.2%)
S1 Q9	What is the recommended annual effective dose of fingers limit for radiation workers in Sri Lanka, as per national regulations?	23 (45.1%)	28 (54.9%)
S1 Q10	What is the primary purpose of radiation protection in radiotherapy?	3 (5.9%)	48 (94.1%)
Section 2			
S2 Q1	Which of the following is NOT a fundamental principle of radiation protection?	0 (0.0%)	52 (100.0%)
S2 Q2	What is the most effective way to reduce radiation exposure to patients and staff in a radiation therapy department?	1 (2.0%)	49 (98.0%)
S2 Q3	What is the purpose of a radiation safety committee in a radiation therapy department?	13 (25.0%)	39 (75.0%)
S2 Q4	What is the primary purpose of a personal radiation monitor, such as a TLD, in a radiation therapy department?	0 (0.0%)	51 (100.0%)
S2 Q5	How often should RTs perform quality assurance tests on the radiation therapy equipment to ensure accurate and safe treatment delivery?	17 (32.7%)	35 (67.3%)
S2 Q6	What is the primary purpose of using pocket dosimeter during radiation therapy procedures?	6 (11.5%)	46 (88.5%)
S2 Q7	What are the standard precautions that RTs should follow to minimize radiation exposure?	26 (50.0%)	26 (50.0%)
S2 Q8	What is the appropriate way to handle radioactive materials during radiation therapy procedures?	20 (39.2%)	31 (60.8%)
S2 Q9	How should RTs handle spills or leaks of radioactive materials?	3 (5.8%)	49 (94.2%)
S2 Q10	What is the appropriate measure to prevent accidental exposure of RTs to ionizing radiation in an external beam unit?	30 (57.7%)	22 (42.3%)
Section 3			
S3 Q1	Which of the following best defines the "prescribed dose" in radiotherapy?	15 (29.4%)	36 (70.6%)
S3 Q2	In radiotherapy, what is the purpose of a "dose prescription"?	4 (8.0%)	46 (92.0%)
S3 Q3	What is the concept of "dose fractionation" in radiotherapy?	2 (3.8%)	50 (96.2%)
S3 Q4	What is the typical fractionation schedule for a standard external beam radiotherapy treatment?	0 (0.0%)	52 (100.0%)
S3 Q5	Which of the following dose prescription methods is based on the radiation dose required to control a specific percentage of tumor cells?	9 (17.6%)	42 (82.4%)
S3 Q6	What is the purpose of "dose constraints" in radiotherapy treatment planning?	5 (9.6%)	47 (90.4%)
S3 Q7	When is the concept of "dose-volume histogram" (DVH) most commonly used in radiotherapy treatment planning?	8 (15.7%)	43 (84.3%)

Table 3 shows the scores concerning general radiation protection were high among individuals with a bachelor's degree (81.95 ± 14.42) and those with working experience of less than 5 years (72.73 ± 25.01). In relation to safety practices followed by RTs, scores were high among individuals with a Higher Diploma (73.06 ± 12.63) and those with working experience exceeding 20 years (74.07 ± 13.41). Similarly, scores pertaining to the radiotherapy treatment doses were high among individuals with a Higher Diploma (83.70 ± 20.00) and those with working experience exceeding 20 years (88.15 ± 16.59). However, high knowledge of radiation protection was observed in individuals holding bachelor's degrees (77.01 ± 9.60) and in those with 10-20 years of working experience (74.28 ± 13.32).

	n	Section 1	Section 2	Section 3	Total Score
Highest qualification					
Higher Diploma	36	61.54 ± 27.84	73.06 ± 12.63	83.70 ± 20.00	71.09 ± 13.92
BSc	13	81.95 ± 14.42	70.26 ± 15.00	82.56 ± 21.35	77.01 ± 9.60
MSc	3	57.69 ± 6.66	58.89 ± 23.41	64.44 ± 30.79	59.62 ± 7.76
Total	52	66.42 ± 25.80	71.54 ± 13.98	82.31 ± 20.95	71.91 ± 13.15
Working experience					
<5	11	72.73 ± 25.01	69.39 ± 17.05	81.82 ± 20.02	73.08 ± 13.12
5-10	9	61.11 ± 27.36	66.67 ± 15.81	76.30 ± 24.97	66.67 ± 12.56
10-20	23	70.40 ± 25.89	73.48 ± 12.08	82.61 ± 21.90	74.28 ± 13.32
>20	9	53.85 ± 23.63	74.07 ± 13.41	88.15 ± 16.59	69.64 ± 13.68
Total	52	66.42 ± 25.80	71.54 ± 13.98	82.31 ± 20.95	71.91 ± 13.15

Note: SD. Standard deviation.

Table 3. Relationship between demographic data and scores (Score, Mean ± SD).

Table 4. Non-parametric analysis of the demographic data and the scores.

	n	values	Section 1	Section 2	Section 3	Total score
Age	-	*p* - value	0.28	0.86	0.88	0.59
Educational qualification						
Higher diploma	36		23.81	27.74	27.29	25.57
BSc	13	Mean	35.73	25.38	26.54	32.85
MSc	3	rank	18.83	16.50	16.83	10.17
		p - value	0.03	0.44	0.48	0.05
Working experience						
<5	11		30.82	24.45	25.95	28.23
5 – 10	9	Mean	23.11	21.94	23.44	19.11
10 – 20	23	rank	28.89	27.74	26.65	29.80
>20	9		18.50	30.39	29.83	23.33
		p - value	0.21	0.61	0.82	0.29

Table 4 was presented for the non-parametric analysis of demographic data and the scores among the study sample. According to the table, no correlation was observed between age and section 1 ($p = 0.28$), section 2 ($p = 0.86$), section 3 ($p = 0.88$), and total score ($p = 0.59$) as determined by Spearman's correlation. A significant difference was observed in the mean rank score of section 1 ($p = 0.03$) concerning educational qualifications. The mean rank score

for bachelor's degree holders was 35.73, while the mean ranks score for higher MSc and diploma holders were 23.81 and 18.83, respectively. It was found that the general radiation protection mean rank score of bachelor's degree holders was superior to that of higher diploma holders and MSc holders. No significant difference was found in the mean rank score of section 2 ($p = 0.44$) and section 3 ($p = 0.48$) based on educational qualifications. A significant difference was observed in the mean rank scores of the total score ($p = 0.05$) across educational qualifications. The mean rank score for bachelor's degree holders was 32.85, while for higher diploma holders and MSc holders, it was 25.57 and 10.17, respectively. Consequently, knowledge of radiation protection was found to be better among bachelor's degree holders and higher diploma holders compared to MSc holders. With p-values exceeding 0.05, no significant difference was observed in the mean rank score of section 1 ($p = 0.21$), section 2 ($p = 0.61$), section 3 ($p = 0.82$), and the total score ($p = 0.29$) based on working experience.

IV. DISCUSSION

This study investigated the assessment of the level of radiation protection knowledge and awareness among RTs in Sri Lanka. The radiation protection knowledge and awareness were investigated in three fields including general radiation protection, safety practices followed by RTs, and radiotherapy treatment doses. The study explored the correlation between knowledge of radiation protection and factors such as age, work experience, and education qualifications.

The results of the study showed a significant relationship between educational background and section 1 ($p = 0.03 < 0.05$) as well as the total score ($p = 0.05$). Specifically, higher educational qualifications were linked to increased section 1 score and total score up to the bachelor's degree level. The results of this study are consistent with that of Kargar et al. (2016) who revealed that there was a positive correlation relationship between radiation awareness and educational qualification ($p = 0.034 < 0.05$). Another study by Mojiri et al. (2011) showed that there was a statistically significant relationship between awareness of dose limit and radiographers' education level ($p = 0.008$). Another similar study by Saeed et al. (2018) reported that there was a difference between radiation protection knowledge and educational qualification of the radiographers which is less than the *p* value of significance ($p = 0.005 < 0.05$). Further, Fatahi-Asl et al. (2013) argued that there is a relationship between radiation protection knowledge scores and associate and bachelor's degree qualifications ($p = 0.0001 < 0.05$). However, statistical analysis of the data of Dehghani et al. (2014) contrasted with this study and revealed that there was no relationship between the radiation protection knowledge and educational level ($p > 0.05$). Nevertheless, it is noteworthy that pursuing an MSc degree was associated with a decrease in both section 1 and total score, the smaller sample size might have influenced the statistical analysis, potentially leading to skewed results. A larger and more diverse sample could offer a clearer understanding of how educational qualifications relate to knowledge of radiation protection. Furthermore, it's crucial to note that MSc programs not directly linked to fields like radiology or radiation therapy might lack comprehensive coverage of radiation protection topics, potentially contributing to lower awareness among graduates. Additionally, the decrease in section 1 scores and total score among MSc degree holders could be reflected in a potential 'knowledge gap' phenomenon. Sometimes, individuals with higher academic qualifications might overestimate their understanding of certain topics or might not prioritize learning about subjects they perceive as less relevant to their specific area of study. Interestingly, section 2 and section 3 did not show any significant correlations with educational qualifications, it was possible that section 1 and section 2 were influenced more by on-the-job training, experience, and adherence to established protocols rather than formal education. Moving forward, enhancing radiation protection education in undergraduate programs could address these disparities and improve safety practices among RTs.

This study indicated that there is no significant difference between the working experience and the knowledge of radiation protection, on the other hand, age was not correlated. This study results contrasted the study results of Dehghani et al. (2014) showed that the results represented age between 20-30 years had a higher level of radiation protection awareness than other age groups. Another study by Mojiri et al. (2011) stated that a statistically significant relationship between working experience ($p = 0.03 < 0.05$) and awareness of radiation effects revealed that the radiographers with low experience had less knowledge about radiation effects. Another similar study carried out by Saeed et al. (2018) revealed that there is a statistically significant difference between radiation protection knowledge ($p = 0.000 < 0.05$) and years of clinical practice. Moreover, the statistical analysis of the data of Saeed Shah et al. (2007) indicated that 88% of the score found in 16-20 years of working experience group, which had scores higher than all other groups showed the educational qualification and working experience in the medical radiation science profession affects the radiation protection awareness level. Drastic training initiatives might be implemented by organizations to ensure that employees, regardless of their tenure, are well-versed in radiation protection protocols. The absence of a correlation of age to the knowledge of radiation protection might have implied that age was not a determining factor in one's ability to work out complex scientific concepts such as radiation protection.

The knowledge of radiation protection was studied in this research, although it might not represent the first

investigation conducted on this topic in Sri Lanka. However, this might be the first investigation on RTs population. However, it is presumed that the study will be crucial in improving the situation of radiation protection knowledge and awareness among RTs in Sri Lanka. Anyhow the limitations of this study played a crucial role in the assessment of radiation protection knowledge and awareness. This study was conducted with a small sample (n = 52) and a smaller number of (n = 3) MSc-qualified RTs participating in the research. A larger number of samples from different institutions may improve the results of this study.

V. CONCLUSION

This study verified that the overall score of radiation protection knowledge and awareness among RTs in Sri Lanka was quite satisfactory (Table 3). Remarkably, the RTs' awareness about their knowledge of radiation protection is necessary. This study has provided valuable insights into the level of radiation protection knowledge and awareness. A descriptive cross-sectional survey was utilized as the research approach, it was possible to get a picture of the radiation therapy workforce and provide insight into several different factors, including safety procedures, radiation protection expertise, and demographics.

The findings highlight both areas of proficiency and potential gaps in knowledge among RTs. Moreover, the study elucidates the correlation between demographic factors such as educational qualifications and working experience with adherence to knowledge of radiation protection and practices. Bachelor's degree holders exhibited higher levels of knowledge in general radiation protection compared to those with higher diploma qualifications or master's degrees (Table 3, Table 4). Additionally, those with longer working experience, particularly exceeding 20 years, showed better adherence to safety practices and understanding of radiotherapy treatment doses (Table 3). These comparisons offer context and further support for the present study's observations. However, radiation protection knowledge and awareness should be improved to protect the patient and RTs.

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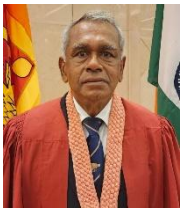
AUTHOR BIOGRAPHIES

I am M. R. M. Anaas, a BSc (Hons) Radiotherapy graduate from KDU. My research interests encompass brachytherapy, external beam radiotherapy, radiation safety, and dosimetry. I have gained clinical experience through training at leading institutions, including Apeksha Hospital Maharagama and National Hospital Kandy. Driven by a passion for advancing the field of radiotherapy, I am committed to enhancing patient care and safety while contributing to innovative research and clinical practices in radiation oncology.

Miss. W. W. Theekshana Nethmini is a graduate who completed her BSc (Hons) in Radiotherapy at KDU. Passionate about research in medical imaging, radiation safety, and dosimetry. She is also actively studying Human Resources Management. With clinical training at esteemed institutions such as Apeksha Hospital Maharagama, National Hospital Kandy,

Teaching Hospital Karapitiya, AOI at Asiri Surgical Hospital, and Ceylinco Healthcare Centre, she is dedicated to advancing her knowledge in both radiotherapy and HR, aspiring to contribute to healthcare and management sectors.



Mr. H. K. A. Dharmasiri began his career as a Radiation Therapist in 1974, advancing to Chief Radiation Therapist at the National Cancer Institute Maharagama. He trained apprentices and coordinated a radiotherapy degree program at the University of Peradeniya. After roles at PNG University of Technology, he returned to KDU as a Senior Lecturer until 2024. He holds a bachelor's and master's degree in radiotherapy physics from the University of Colombo.

Ranga Tudugala is a Sri Lankan therapeutic radiographer currently working at National health service United Kingdom. He holds an MSc in Biostatistics and Medical Physics, with expertise in radiotherapy. he has authored multiple publications and has a background in teaching within the field of Allied Health Sciences.

Evaluation of Inter-fractional Geometric and Dosimetric Variations in Gynaecology Brachytherapy based on C-arm X-ray Images in Carcinoma of Cervix at Apeksha Hospital Maharagama

SP Hapugoda[1#], HKA Dharmasiri[1], R Tudugala[1], and J Balawardane[2]

[1]*Department of Radiography and Radiotherapy, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Sri Lanka*
[2]*Department of Oncology, University Hospital KDU, Sri Lanka*

[#]37-rtp-0002@kdu.ac.lk

Abstract *— Treatment reproducibility is a key aspect of accurate radiotherapy to achieve better target coverage and normal organ sparing. Uniform protocols for these procedures should be maintained to achieve this. Partial coverage of the target leads to recurrence of the tumour and over exposure of Organs at risk (OAR) results in severe complications. Therefore, close consideration of the doses and volumes during the planning process and consideration of inter-fractional treatment variations are essential to minimize such complications. The aim of this study is to assess the relationship among inter-fractional technical, geometrical, and dosimetric variations and to determine the causes for these variations in gynaecology brachytherapy for carcinoma of cervix. A total of 211 subjects who have completed High Dose Rate (HDR) brachytherapy between January 2022 and January 2023 at Apeksha Hospital Maharagama were selected for this study. Data were obtained from the logbook and daily dose profile which is available in the HDRplus 3.0 software. The data included treated volumes, delivered doses, number of activated dwell points, applicator distances and number of packs utilized. The data were further analysed using IBM SPSS statistics software (version 28.0). According to the results, correlations between treated volume variations and applicator variations are mostly significant, and the correlation with tandem is highly significant. Correlations between bladder dose variations and applicator variations are mostly insignificant while the correlations between rectal dose variations and applicator variations are totally insignificant. The relationship between dosimetric variations of both the bladder and the rectum are highly significant with the variations in the number of gauze packs utilized inter-fractionally. In conclusion, geometric variations were predominantly affected by applicator variations of the tandem while bladder and rectal doses were less affected by applicator variations and were mostly affected by gauze packs.*

Keywords *— radiotherapy, high dose rate brachytherapy, treated volume, bladder dose, rectal dose, gauze packs, applicators*

I. INTRODUCTION

Cervical carcinoma is the 4th most frequent type of cancer and 2nd leading cause of death among all cancers reported among women globally (Ncane *et al.*, 2023). Nearly 32,000 cases are diagnosed with cervical cancer each year and statistics state cervical cancer is the 4th most frequent cancer in Sri Lanka *(Iqbal and Joseph, 2023)*. This cancer occurs as an abnormal cell growth in the lining of the cervix. The most frequent type of cervical cancer is squamous cell carcinoma (SCC) and less commonly adenocarcinoma which occur in the glandular tissue. The main carcinogen for cervical cancer is Human Papillomavirus (HPV) which transmits during sexual contact. Other causes like smoking, multiple sexual partners, parity, early coitus, and childbirth also contribute to carcinoma of the cervix. Early diagnosis of cervical cancer increases survival rate as rectal and bladder invasion can be minimized at early stages. The average diagnosis age is 49 years. Stage 1 to 4 of carcinoma of the cervix increases the severity respectively.

Usually, patients manifest no symptoms in the precancer stage of cervical cancer. Therefore, regular Pap smears and HPV tests are efficient methods of detection and prevention. Symptoms eventually start to be seen once the cancer cells invade the deepest parts of the cervix and pelvic organs *(CERVICAL CANCER Your Guide, 2021)*. The symptoms include discharge in the vagina, abnormal bleeding in the vagina, and pain and vaginal odor.

Treatment options available in the present setting are surgery, external beam radiotherapy (EBRT), chemotherapy, and brachytherapy. Microinvasive stage disease (not greater than 3 mm deep stromal invasion and no greater than 7 mm diameter.) is treated with vaginal hysterectomy or excisional cone biopsy in young patients which can conserve fertility *(Practical Radiotherapy Planning, 2009)*. Carcinoma of the cervix can be prevented by the HPV vaccine given to both females and males from ages 9 to 26. However, this vaccine is available for people up to 45 years*(CERVICAL CANCER Your Guide, 2021)*.

Brachytherapy is a radiation treatment technique where the radioactive source is kept at a short- distance from the malignant disease. The radioactive source is a small, sealed,

encapsulated source and common radioisotopes used are Co-60, Cs-137, Ir-192, I-125, and Pd-103. Co-60 is the radioisotope used in the current setting of Sri Lanka. The advantages of brachytherapy include a more confined dose delivery to the target, a sharp dose fall-off outside the target volume that minimizes the dose to normal tissue, and better conformal therapy. However, the disadvantages of brachytherapy are that it can be used only for well-confined tumours, is suitable only for compact lesions, and is very labour intensive *(Suntharalingam, Podgorsak and Tolli, 2006)*.

Intracavitary brachytherapy is a widely used effective radiation treatment method for locally advanced gynaecological tumors worldwide. Brachytherapy is given either alone or combined with EBRT. The advantage of this treatment modality is a high dose can be delivered in 2-3 fractions without resulting in severe complications. Brachytherapy can be given in several ways as temporary treatments like high dose rate (HDR) (>12 Gr/h) and low dose rate (LDR) (0.4 – 2 Gy/h) or as permanent treatments by placing an implant inside the body. The temporary method is the treatment option used for cervical cancers *(Suntharalingam, Podgorsak and Tolli, 2006)*. As usual high dose rate brachytherapy is currently used in Sri Lanka. Hence highly accurate dosimetry for the target volume as well as for risk organs is necessary. Also, accurate positioning of the source is important to prevent geographical misses. The major benefit claimed for HDR brachytherapy application is the chance to achieve a better physical dose distribution by better packing and careful positioning due to the short duration of treatment. Such practices are based on a two-dimensional treatment plan based on two orthogonal radiographs taken soon after the patient's positioning.

The acquired orthogonal X-rays are used to plan the HDR treatments using the Manchester system. The planning process starts with the desired dose distribution and then the dwell points and dwell times are taken to produce that distribution. Dwell time depends on the half-life of the source. These plans frequently cover a considerable volume of the normal tissues including the risk organs to their tolerances. Therefore, planned weights should be optimized.

The Manchester system is used in current brachytherapy practices. This system can be described by doses to four points; Point A, Point B, Rectal point, and Bladder point *(Sharma, 2011)*. The dose is prescribed to point A as the dose-limiting point. Point A can be described as 2 cm lateral from the midline and 2 cm superior in relation to the cervical os along the tandem. Point B is defined as 2cm superior to the cervical os and 5cm lateral to the midline. (see Figure 1). Point B provides information about the lateral dose fall-off which is important when considering normal tissue preservation. Point A depends on the source instead of the anatomical structure. Therefore, point A may be situated internally to the tumor or externally to the tumor. Practically in most patients, the uterus tilts towards a side. In that case point A follows the tilt of the uterus but point B is independent of this tilt therefore, it does not change *(Thomadsen, 2014)*. A reference point for the bladder and rectum is defined separately to account for the dose to those risk organs. The bladder point is posterior to the catheter balloon filled with 7 mL of contrast solution. The rectal point is 0.5 cm posterior to the most posterior packing or posterior surface of the ovoid *(Practical Radiotherapy Planning, 2009)*. The aim is to provide a pear-shaped dose distribution obtained using Green's theorem by defining point A. The pear-shaped dose distribution should be replicated in each fraction which can be altered according to the patient's anatomy and the implants used.

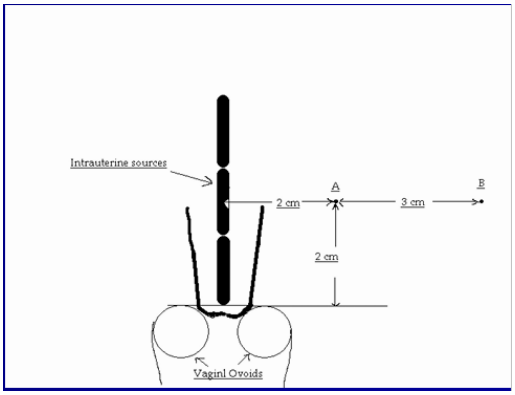


Figure 1. Point A and Point B according to the Manchester system *(Sharma, 2011)*.

Complications occur due to the risk of organ irradiation. The risk organs that surround the cervix are the bladder, rectum, and sigmoidal colon. The treatment should not exceed the tolerance doses of the organs which are 65 Gy, 60 Gy, and 45 Gy respectively *(Practical Radiotherapy Planning, 2009)*. Most frequent clinical complications occur due to high doses delivered to a portion of the rectum and bladder can be minimized by increasing the distance between the source and the critical organs as high as possible *(Suntharalingam, Podgorsak and Tolli, 2006)*. This is performed using surgical gauze packs to keep the structures away from the applicator. Other than the risk organs, irradiation of the vagina and vulva causes acute side effects like erythema, soreness, and presentation of discharge. Common acute side effects that occur in brachytherapy are pain, swelling, bruising, bleeding, fatigue, diarrhea, nausea, anemia, etc. Discomfort on the spot of irradiation also results in short-term symptoms like urinary retention, incontinence, or pain of urination. Common late side effects are narrowing of the vagina and loss of lubrication, radiation cystitis, radiation colitis, early or sudden menopause, lymphedema, etc. *(CERVICAL CANCER Your Guide, 2021)*

This study aims to identify the factors that can cause inter-fractional variations in current brachytherapy treatments for

cervical cancers by evaluating dosimetric and geometric variations in current practice at Apeksha Hospital, Maharagama.

II. METHODOLOGY

This retrospective, quantitative study was conducted among 211 cervical cancer patients who have completed treatments by HDR brachytherapy between 2022 January and 2023 January at Apeksha Hospital Maharagama (AHM), Sri Lanka. Considering the purposive sampling method, approximately a group of 111 patients prescribed with only two treatment fractions, and 100 patients prescribed with three fractions, and as a total, 211 cervical cancer patients were selected. All considered patients were treated for HDR intracavitary brachytherapy at AHM, Sri Lanka, and the data were collected during three months from August to October 2023 for this study. The average bladder doses, rectal doses delivered in each treatment fraction, and technical details such as the number of activated dwell points and applicator distances of each applicator (tandem, right ovoid, left ovoid) were collected from the daily dose profile of every treatment fraction, and the volumes that were exposed by the prescribed dose was obtained from the dose volume histogram (DVH) of each fraction which was recorded in the HDRplus 3.0 software at AHM. The number of gauze packs used for the treatment was obtained from the manually recorded logbook. After obtaining the data, variations were calculated and further analysed using the IBM SPSS statistics software version 28 package. Mainly, correlations between dose variations, and technical factors, volume variations, and technical factors were assessed. A paired sample t-test and a Wilcoxon signed rank test were used to account for the relationship between the delivered dose to the rectum and bladder and surgical packs.

III. RESULTS

A non-parametric correlation test was performed to assess the relationship between volume and dose variations with applicator variations as the data samples did not show a normal distribution. The Spearman rank-order correlation coefficient was used accordingly.

A. Relationship between inter-fractional treated volume variations with the variations in the number of dwell points and variation of applicator distances of each applicator.

Technical factors can contribute to volume uncertainties (Otani *et al.*, 2018). To assess that, the correlation between inter-fractional treated volume variations and applicator variations was considered using the Spearmen rank-order correlation test.

Table 1. Correlations between inter-fractional treated volume variations and variations in number of dwell points.

	Frac. 1 and 2	**Frac. 2 and 3**	**Frac. 1 and 3**
Tandem	<0.001	<0.001	<0.001
Right Ovoid	<0.001	0.124	0.011
Left Ovoid	<0.001	0.184	0.015

Table 2. Correlations between inter-fractional treated volume variations and variations in applicator distance.

	FRAC. 1 AND 2	**FRAC. 2 AND 3**	**FRAC. 1 AND 3**
Tandem	<0.001	<0.001	<0.001
Right Ovoid	0.003	0.075	0.003
Left Ovoid	0.002	0.072	0.004

B. Relationship between inter-fractional dose variations to rectum and bladder with the variations in the number of dwell points and applicator distances in each applicator.

Correlation between variations of the doses delivered to the rectum and bladder with applicator variations were take using Spearmen rank-order correlation to identify whether the variations in the applicators would affect the delivered doses.

Table 3. Correlations between inter-fractional bladder dose variations and variations in number of dwell points.

	FRAC. 1 AND 2	**FRAC. 2 AND 3**	**FRAC. 1 AND 3**
Tandem	0.544	0.542	0.034
Right Ovoid	0.075	0.591	0.251
Left Ovoid	0.037	0.948	0.386

Table 4. Correlations between inter-fractional bladder dose variations and variations in applicator distances.

	FRAC. 1 AND 2	**FRAC. 2 AND 3**	**FRAC. 1 AND 3**
Tandem	0.684	0.309	0.009
Right Ovoid	0.039	0.316	0.132
Left Ovoid	0.081	0.783	0.355

Table 5. Correlations between inter-fractional rectal dose variations and variations in number of dwell points.

	FRAC. 1 AND 2	FRAC. 2 AND 3	FRAC. 1 AND 3
Tandem	0.256	0.581	0.443
Right Ovoid	0.199	0.312	0.525
Left Ovoid	0.241	0.115	0.991

Table 6. Correlations between inter-fractional rectal dose variations and variations in applicator distances.

	FRAC. 1 AND 2	FRAC. 2 AND 3	FRAC. 1 AND 3
Tandem	0.191	0.280	0.443
Right Ovoid	0.568	0.367	0.469
Left Ovoid	0.420	0.423	0.766

C. Relationship of inter-fractional variations in dose delivery to the bladder and rectum with the variations in the number of gauze packs utilized.

To assess this relationship, a Wilcoxon signed rank test was performed between fractions 1 and 2 as the distribution was not normal. Paired sample t-test was performed between fractions 2 and 3 and between fractions 1 and 3.

Table 7. Relationship between inter-fractional rectal and bladder dose variations and variations in the number of gauze packs utilized.

FRACTIONS	BLADDER	RECTUM
Fraction 1 and 2 (Wilcoxon signed rank test)	<0.001	<0.001
Fraction 2 and 3 (Paired sample t-test)	<0.001	<0.001
Fraction 1 and 3 (Paired sample t-test)	<0.001	<0.001

IV. DISCUSSION

Treated volume in brachytherapy is an important aspect in terms of tumor coverage and normal tissue irradiation. Therefore, maintaining a treatment volume with the least uncertainties is a crucial aspect of brachytherapy. Most of the correlations revealed were highly significant between applicator variations and the treated volumes (see Table 1 and Table 2). However, the number of dwell points in the right and left ovoid correlation with the volume variation was insignificant in the comparison between fraction 2 and fraction 3 in this study, which was an unexpected observation (see Table 1). A similar pattern was observed when considering the correlation between volume variations with the applicator distance variations in all three applicators (see Table 2).

Dose delivered to the bladder and rectum should be considered as they are critical organs that should be preserved *(Practical Radiotherapy Planning, 2009)*. Therefore, the fractional doses should not exceed the tolerance level which is 80% of the prescribed dose to the bladder and 70% of the prescribed dose to the rectum. Doses delivered to the rectum and bladder in all patients of the sample were within the tolerance level and no violations were evident. However, to identify whether the variations in the applicators would affect the delivered doses, the correlations between doses received by the rectum and bladder with applicator variations were obtained. Most of the results showed an insignificant correlation with the variations of rectal and bladder doses (see Table 3, Table 4, Table 5, Table 6). The dose delivered to the rectum might not be affected by the number of dwell points and applicator distances as the correlation was revealed to be insignificant (see Table 5 and Table 6). Meanwhile, the delivered dose to the bladder was manifested to be affected by the applicator distance and number of dwell points as the correlation with dwell points variation of the left ovoid (see Table 3) and applicator distance variation of the right ovoid (see Table 4) was significant between fraction 1 and fraction 2. The bladder dose variations that occurred between fraction 1 and fraction 3 also showed a significant correlation with the number of dwell points and applicator distance variations only in tandem (see Table 3 and Table 4) but on the contrary, the bladder dose variation that took place when progressing from fraction 2 to fraction 3 and correlations except for the values mentioned above demonstrated an insignificant correlation with the number of dwell points and applicator distance variations.

Sterilized gauze packs were utilized to maintain a sufficient distance between the critical organs and the applicators. Therefore, the number of gauze packs could impact the dose delivered to the critical organs. Mainly, vaginal gauze packing was a technique that was widely used especially in rectal dose reduction according to *(Sawada et al., 2023)*. It was manifested in the results as the dose variations of the bladder and rectum between all three fractions demonstrated a significant difference when the number of packs changed and remained constant (see Table 7). This indicated that the bladder and rectal dose variations differed significantly

depending on whether the number of packs changed or remained constant.

V. CONCLUSION

Treated volume was evident to be mostly affected by dwell points and applicator distances as most of the correlation results were significant, especially in tandem between all three fractions. Therefore, inter-fractional applicator variations have an impact on geometric variations. The delivered dose to the bladder was less affected by applicator variations since only two values were revealed to be significant and meanwhile, all the values between doses delivered to the rectum and applicator variations were insignificant. Therefore, inter-fractional dosimetric variations were less affected by applicator variations instead, mostly affected by gauze packs as the results showed a highly significant relationship between the doses delivered to the rectum and bladder and gauze packs between all three fractions.

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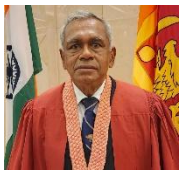
AUTHOR BIOGRAPHY

Miss S.P.Hapugoda is a graduate in BSc. (Hons) in Radiotherapy at General Sir John Kotelawela Defense University, Sri Lanka.



Mr. HKA Dharmasiri began his career as a Radiation Therapist in 1974advancing to chief Radiation Therapist at National Cancer Institute Maharagama. He trained apprentices and coordinated a Radiotherapy degree programme in University of Peradeniya. After roles at PNG University of Technology, He returned to KDU as a Senior Lecturer until 2024.He holds a Bachelor's and Master's degree in Radiotherapy Physics from the University of Colombo.

Mr. Ranga Tudugala is a Sri Lankan Therapeutic Radiographer currently working at National Health Service United Kingdom. He holds an MSc in Biostatistics and Medical Physics, with expertise in Radiotherapy. He has authored multiple publications and has a background in teaching within the field of Allied Health Sciences.

Prof. Jayantha Balawardena is a distinguished oncologist with over four decades of experience in the field of oncology and radiotherapy. Prof. Balawardena has held several prestigious positions throughout his career, including Senior Consultant Oncologist and Head of the Department of Radiotherapy and Oncology at the Cancer Institute in Maharagama, Sri Lanka, Senior Lecturer and Professor in Oncology at the General Sir John Kotelawala Defence University. He currently serves as the Chancellor of the Uva Wellassa University. His extensive training includes overseas experience in the UK, South Africa, and advanced courses in nuclear medicine and breast conservation. A dedicated leader, Prof. Balawardena has served as the President of the Sri Lanka College of Oncologists and held various advisory roles in national health programs. He has received several accolades, including the Sri Lanka Sikhamani National Honor and a Cancer Care Excellence Award.

Is Discrete Incremental Meta Docking (DIMD) the Key to Success in Molecular Docking-Based Drug Discovery? A Comparison of the Results of the Novel Vinca Derivative VADRPA01

HMAJ Halahakoon

Department of Pharmacy, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Sri Lanka

halakoonhmaj@kdu.ac.lk

Abstract *— Determining the crystal structure of vinca-site inhibitors in complex with the tubulin heterodimer is crucial for understanding binding modes and guiding the design of novel microtubule inhibitors targeting the vinca binding domain. However, the lack of a universally validated methodology for dataset preparation and protein-ligand validation complicates the comparison and reproduction of docking results. The present study addresses this issue by evaluating the molecular docking results using the Discrete Incremental Meta Docking (DIMD) technique. The DIMD method facilitated the identification of the best docking pose for a novel vinblastine derivative, VADRPA01, with a binding affinity of -15.416 kcal/mol (a 47.74% enhancement) and an inhibition constant of 0.0051 nM, compared to its best rigid docking pose (-10.8 kcal/mol) obtained through a general docking procedure. Crystallized water at the vinca binding site of the native vinblastine-5J2T (tubulin) complex was found to stabilize VADRPA01 within the binding domain. Molecular dynamics studies revealed that flexible amino acid residues in the receptor binding pocket contributed to the reduction of binding energy by forming hydrogen bonds with PHE351, LYS336, ALA333, and ASN329 on the alpha chain of the tubulin heterodimer. Additionally, the calculated protein-ligand binding affinities using MMPB(GB)SA indicated a total binding energy of -27.15 kcal/mol, confirming the stability of the 5J2T-VADRPA01 complex. The optimal docking pose of VADRPA01, derived from the hydrated flexible docking procedure, showed an RMSD of 1.5020 Å compared to the native vinblastine-5J2T complex. These advancements in the docking procedure have identified the most favourable docking pose for VADRPA01, supporting further drug discovery studies of vinca derivatives.*

Keywords *— Vinca Alkaloids, Molecular Docking, Tubulin, DIMD, Drug Discovery, gmxMMPBSA*

I. INTRODUCTION

In-silico drug design, a core field in bioinformatics and pharmaceutical science, leverages computational methods to accelerate modern drug discovery. This approach spans the drug development pipeline, from initial lead generation to clinical stages, largely relying on molecular docking to simulate protein-ligand interactions and assess binding affinity. A successful docking-based drug discovery depends heavily on defining the accurate conformations of protein-ligand complexes and evaluating affinity through scoring methods. Bioinformatics enhances in-silico drug design by providing critical tools for analyzing biological data, predicting drug-target interactions, and modelling molecular structures (Feyza Maden S, *et al.,* 2023; Corbeil *et al.,* 2012; Mohan *et al.,* 2021).

Molecular docking has become essential in predicting protein-ligand complex structures, involving two key processes: sampling, which explores the ligand's position, conformations, and interactions with the protein, and scoring, which evaluates binding affinities. Although algorithms often predict binding poses accurately, the reliable estimation of binding affinities and the influence of interface water molecules remain significant challenges. Properly accounting for protein-centric water molecules is crucial, as crystallographic studies reveal their positions and role in bridging protein-ligand interactions (Feyza Maden S, *et al.,* 2023; Leelananda *et al*., 2016).

While commercial and open-source docking programs are efficient and widely adopted, their success is not solely determined by technical advances. Fundamental challenges persist, such as managing protein flexibility, identifying binding sites, addressing solvation effects, and accurately predicting binding affinities. These complexities highlight ongoing limitations in docking-based drug discovery *(*Sethi *et al., 2020;* Hu *et al., 2018).* Data set preparation is pivotal for successful molecular docking-based drug discovery, directly influencing the accuracy of binding affinity predictions. The robust data set preparation mitigates errors from docking pose generation. Numerous studies indicate that docking success rates depend on scoring function selection, target specificity, input parameters, and success criteria, complicating cross-study comparisons and often leading to conflicting conclusions. A critical challenge for the field is the lack of a universally accepted standard test set, hindering the reproducibility and comparability of docking results (Corbeil *et al.,* 2012). Preparation errors can cause over 20% variability in success rates, underscoring the need for standardized protocols. In the

context of tubulin-binding vinca alkaloids, structural determination of vinca-site inhibitors aids in understanding binding modes, offering a basis for designing new inhibitors (Jordan & Wilson, 1998). This study evaluates molecular docking outcomes for VADRPA01, a novel proposed vinca alkaloid derivative, using diverse data processing methods across AutoDock, AutoDock Vina, DOCK6, and MOE.

II. MATERIALS AND METHODS

The RCSB PDB database offers an extensive experimental binding affinity dataset for crystallized tubulin complexes with various ligands, including vinblastine (PubChem ID 13342), which served as a reference for developing the derivative VADRPA01. Seven crystallized structures 1z2B, 5J2T, 8cle, 7z7d, 8clh, 4eb6, and 5bmv from the RCSB PDB database were used as reference complexes.

This study employed a Discrete Incremental Meta Docking (DIMD) methodology, an advanced approach designed to improve docking accuracy by refining docking poses iteratively, integrating multiple scoring functions, and conducting a meta-analysis to combine results from different simulations. Four docking programs AutoDock4, Vina, DOCK6, and MOE with diverse scoring algorithms were applied.

Crystalized vinblastine-tubulin complexes were analyzed using Discovery Studio version 21.1.0 and MOE version 2022.02 (https://www.chemcomp.com/) for ligand and protein preparation The superimposed tubulin heterodimer with the vinca binding site is shown in Figure 01.

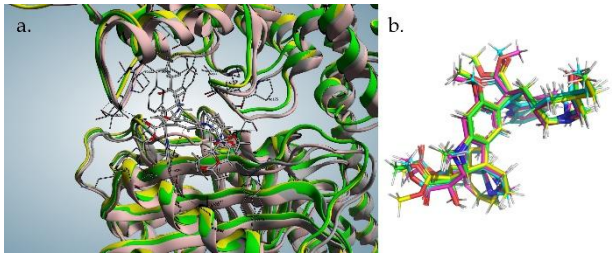


Figure 01. Superimposed crystalized Tubulin molecules were used for the study (vinca binding site view) with respective binding pocket residues.

a. Tubulin molecules, Ash colour - 5J2T receptor; pink – 7z7d; green – 8cle, yellow – 8clh; Ash colour ligand – vinblastine complexed to 5J2T molecule. The calculated RMSD values are as follows: 5J2T/7z7d – 0.823 A^0; RMSD 5J2T/8cle – 0.854 A^0; RMSD 5J2T/8clh – 1.305A^0 .

b. Superimposed ligands (Vinblastine) molecule complexed with different Tubulin molecules published in RCSB PDB database.

Root mean square deviation (RMSD) values were calculated for the tubulin backbone and vinblastine ligands. Missing residues in the tubulin-binding pockets were identified and reconstructed using tools like SWISSPDB Viewer, Chimera, and MOE. After addressing structural gaps, the 5J2T complex underwent energy minimization with the CHARMM27 force field, in preparation for future molecular dynamics simulations in GROMACS. Ramachandran plots and B-factor analyses highlighted thermal displacement potentials in specific chains. VADRPA01 was synthesized by modifying vinblastine, replacing the N-bonded -CH_3 group with an aminopyrimidine residue at the dihydroxy catharanthine site. SMILES of the derivative molecule is given below.

SMILES

[H]O[C@]1(C([H])([H])C([H])([H])[H])C([H])([H])[N@@]2C([H])([H])[C@@]([H])(C1([H])[H])C([H])([H])[C@@](C(=O)OC([H])([H])[H])(C1=C(c3c([H])c([H])c([H])c([H])c3N1[H])C([H])([H])C2([H])[H])c1c([H])c2c(c([H])c1OC([H])([H])[H])N(C([H])([H])C1C=CN(N)C=C1)[C@]1([H])[C@]22C([H])([H])C([H])([H])N3C([H])([H])C([H])=C([H])[C@](C([H])([H])C([H])([H])[H])([C@@]23[H])[C@@]([H])(OC(=O)C([H])([H])[H])[C@]1(O[H])C(=O)OC([H])([H])[H]

Importance of the forcefield

The Discrete Incremental Meta Docking (DIMD) protocol was executed using AutoDock4, AutoDock Vina, DOCK6, and MOE, each with distinct force fields. AutoDock 4.2 applies a semiempirical free energy force field and uses grid-based energy evaluations. Vina allows users to select between Vina and Vinardo force fields, with default settings requiring no grid maps or receptor atom charges. MOE features an integrated multiprocessor forcefield engine with open parameterization capabilities. The docking methodology began by isolating vinblastine from tubulin using Chimera. The derivative molecule, VADRPA01, and vinblastine were then docked with a prepared 5J2T tubulin molecule, filling missing segments and applying a rigid receptor-flexible ligand model. The top five solutions from each docking program (20 total) were rescored with AutoDock Vina, clustered by pose similarity, and compared to the native vinblastine-5J2T pose. Docking solutions with RMSD $\leqslant$ 2.5 Å were selected for further analysis. Interaction studies using Discovery Studio and MOE identified key residues critical to the binding. A flexible docking approach optimized these poses by treating key residues as flexible, then redocking with AutoDock Vina using Vina, Vinardo, and AutoDock4 force fields. Subsequent clustering and scoring isolated the most optimal pose, with native vinblastine-tubulin structure analysis revealing key binding-pocket crystallized water molecules affecting binding energy and accuracy.

In the final step, the top docking pose was redocked with the 5J2T molecule using a hydrated flexible docking procedure. AutoDock Vina's AD4 force field was chosen, as Vina and Vinardo do not support hydrated docking. The best pose was selected by docking score, and compared to the native vinblastine docking pose, with protocol success evaluated against trusted databases such as PDBbind. Results are detailed in the Results and Discussion section.

III. RESULTS AND DISCUSSION

Figure 02 showcases the results of 200 rescored docking poses for the VADRPA01 molecule with tubulin, using

AutoDock Vina, ranked by docking score and RMSD relative to the native vinblastine-5J2T complex. These poses were evaluated against the experimental K_i of 0.4 µM for the 1z2b-vinblastine complex, serving as a reference.

The binding free energy (ΔG) distribution of the poses displays a linear correlation with Log Ki values, with approximately 40–45 poses closely matching the reference K_i. From these, 20 poses were selected for further analysis.

Figure 03 compares the key amino acid interactions of both the native vinblastine and VADRPA01 with the 5J2T binding site. Notably, the VADRPA01 ligand interacts with residue LYS336 at a distance of 2.84 Å, compared to 4.16 Å in the native complex, potentially increasing the molecule's binding energy. ASN329 also forms a hydrogen bond with VADRPA01 at 2.84 Å, highlighting crucial contacts that justify the selection of flexible docking for further optimization.

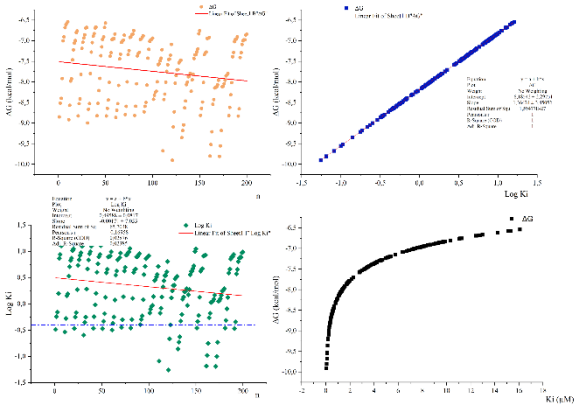


Figure 02. Scatter plots of the docking scores and calculated inhibition constant (log Kd) for selected vina-rescored docking poses for the core.
Inhibition constant (K_i) is calculated according to AutoDock as follows: $K_i = \exp((\text{deltaG} \times 1000.)/(\text{Rcal} \times T)$ where deltaG is docking energy, Rcal is 1.98719 and T is 298.15 K; blue dash line indicates the reference Ki value (0.4 µM) published in PDBbind database.

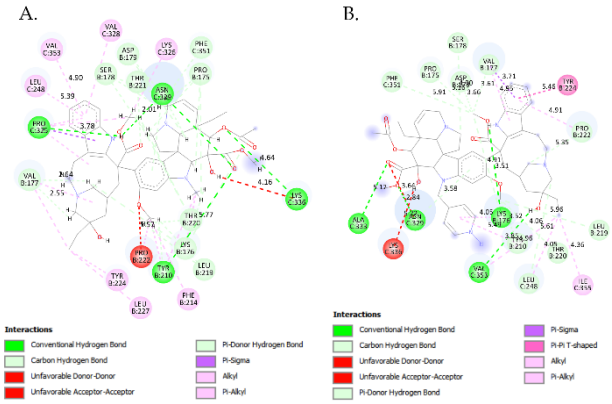


Figure 03. Binding poses of the proposed vinca alkaloid derivative VADRPA01 and native complexed Vinblastine molecule with key residues in the binding pocket shown in 2D view using the rigid receptor docking technique
A. Native complexed mode of the vinblastine with 5J2T; B. VADRPA01 docking pose (binding affinity -10.8 kcal/mol, scoring function is vina)

In the flexible docking step, in chain C VAL C 328, LYS C 326, ASN C 329, VAL C 353, ILE C 355, LEU C 248 and in chain B THR B 220, PHE B 214, LEU B 227, TYR B 224, VAL B 177, ASP B 179, TYR B 210 as the key flexible residues with 32 torsions in total used to enhance binding interactions. This flexible docking conformation yielded a -11.7 kcal/mol binding affinity for VADRPA01, an 8.33% improvement over the rigid docking score of -10.8 kcal/mol, although the VADRPA01 exhibited unfavourable interactions with residues ASN329 and THR224, suggesting some unfavourable overlapping of ligand and residue atoms within the vinca binding pocket.

Recognizing the stabilizing role of crystallized water molecules in the vinblastine complex (with 17 water molecules in the binding site), VADRPA01 underwent a hydrate docking procedure to better approximate native-like conditions. Meeko was used for ligand preparation, and the AutoDock prepare_gpf.py script generated parameters for flexible hydrate docking. The optimal pose from this procedure, visualized in Figure 04, achieved a binding affinity of -15.416 kcal/mol (0.0051 nM K_i), improving affinity by 42.74% compared to the initial rigid docking pose. The calculated RMSD of 1.502 Å from the native pose indicates acceptable alignment for VADRPA01, whose interactions with water and amino acids in the binding pocket are illustrated in Figure 04.

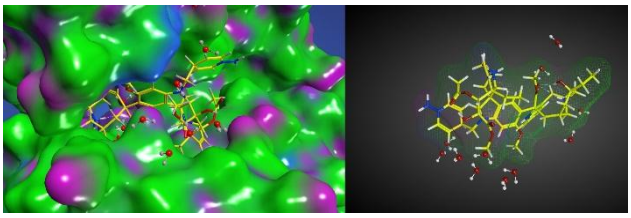


Figure 04. The optimal docking pose of VADRPA01 within the 5J2T binding site, characterized by the active LP electron surface, is generated via the hydrate-flexible residue docking procedure. The left panel depicts the VADRPA01 molecule interacting with the crystallized water molecule in the binding pocket. The right panel shows the isolated VADRPA01 with the crystallized water molecule within the 5J2T binding pocket. The active lone pair surface of the ligand is displayed as a mesh. The binding affinity of this docking pose is calculated to be -15.416 kcal/mol, with a Ki value of 0.0051nM. Surface colour code Green – hydrophobic; blue - mild polar; purple – H-bonding.

These findings confirm that hydrate docking considerably enhances VADRPA01's stability and binding within the vinca domain. The VADRPA01 molecule exhibits six hydrogen bonds with residues PHE351, LYS336, ALA333, and ASN329 on the tubulin C-chain, stabilizing its conformation within the vinca binding site. Notably, residues ASN329 and LYS336, despite their stabilizing hydrogen bonds, exhibit unfavourable interactions in both rigid and flexible docking poses, suggesting complexities in their contribution to overall binding affinity. These hydrogen bonds, being non-covalent interactions, lower the binding energy (−15.416 kcal/mol), enhancing VADRPA01's binding affinity. The presence of ten water molecules within the binding site, forming additional hydrogen bonds with the vindoline and catharanthine

portions of VADRPA01, further amplifies the docking pose's binding affinity (Figure 05).

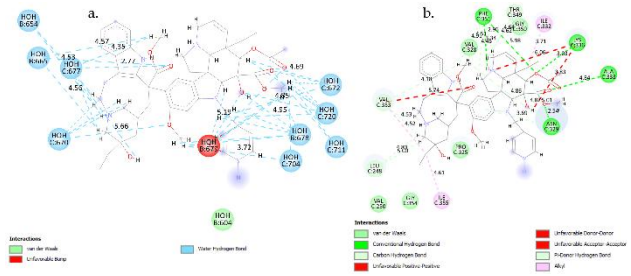


Figure 05. The intricate interactions between various amino acid residues and VADRPA01 within the vinca binding pocket of the 5J2T protein, as identified by the optimal docking pose generated through the hydrate flexible docking technique.
a. Interaction of VADRPA01 with the crystallized water molecule in the binding pocket.

To assess the stability and interaction dynamics of the optimized VADRPA01 pose, molecular dynamics (MD) simulations were conducted using GROMACS 2024. The protein topology was based on the CHARMM27 force field, while the VADRPA01 topology was generated with the SWISSPARAM server. The system was solvated, energy minimized, and subjected to a 100-ps heating phase in the NVT ensemble from 0 to 310 K, followed by 100-ps NPT equilibration, and a 50-ns production run, with atomic coordinates saved every 100 ps. Utilizing the KDU computer cluster, this simulation incorporated the 5J2T tubulin molecule (comprising six heterodimers A–F), crystallized water, and calcium and magnesium ions. The trjconv tool rewrapped and recentered the trajectory data to align with the triclinic unit cell, maintaining system coherence.

Trajectory analyses using VMD revealed that VADRPA01 remained securely within the binding pocket throughout the simulation. Hydrogen bond interactions between VADRPA01, tubulin residues, and crystallized water within the pocket were consistent, indicating that the stability of the initial docking poses was preserved during the MD simulation. Root Mean Square Fluctuation (RMSF) values for VADRPA01 ranged from 0.05 to 0.2 nm, showing minimal positional shifts, while Root Mean Square Deviation (RMSD) plots for both the protein-ligand and side chain-ligand systems indicated fluctuations between 0.2 and 0.8 nm, suggesting robust stability of the docking conformation. These outcomes support that the DIMD methodology effectively optimized VADRPA01's binding to tubulin, potentially enhancing its docking success within the vinca binding site (Figure 06).

Moreover, the influence of water molecules within the binding pocket was critical, stabilizing the VADRPA01 pose at the vinca site. As reflected in RMSF values, protein residue flexibility indicates that the tubulin heterodimers retained structural adaptability throughout the MD run, likely supporting VADRPA01's binding pose maintenance. To estimate the binding free energy with

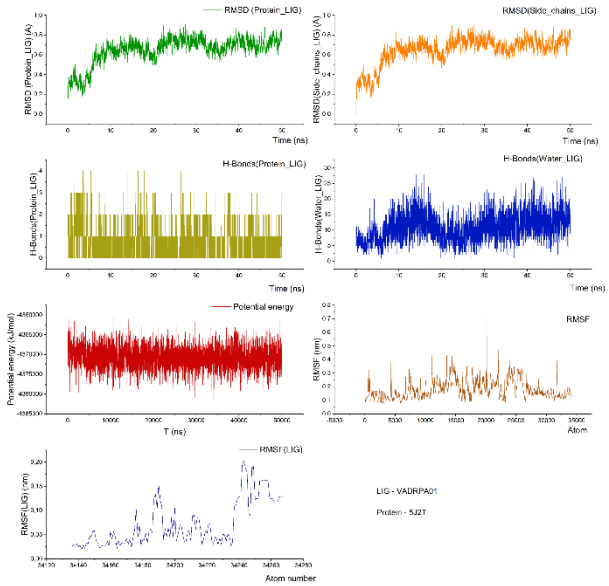


Figure 06. The Molecular Dynamic analysis results of the VADRPA01 optimized docking pose with 5J2T utilizing DIMD method.

precision, the Molecular Mechanics/Poisson-Boltzmann (or Generalized Born) Surface Area (MM/PB(GB)SA) approach was applied, striking a balance between accuracy and computational efficiency for large molecular systems. A detailed binding energy decomposition analysis for individual binding site residues, performed using gmxMMPBSA, offered deeper insights into specific interactions, further elucidating the dynamics between VADRPA01 and tubulin. These findings underscore the DIMD method's effectiveness in achieving an optimal VADRPA01 binding pose within the vinca binding domain, demonstrating that water-mediated interactions and residue flexibility collectively enhance docking stability and binding affinity in this protein-ligand complex.

The preparation and application of alanine scanning are essential for systematically assessing each amino acid residue's role in the function or stability of protein complexes, as executed using the gmxMMPBSA tool in the VADRPA01-5J2T system. The results, summarized and depicted in Figure 07, highlight the binding energy profile of the VADRPA01-5J2T complex generated by the DIMD protocol. With a total binding energy of -27.15 kcal/mol, this system demonstrates a favourable binding interaction that approaches the stability of the native complex (with a binding energy of -28.94 kcal/mol). This similarity implies a robust protein-ligand interaction, with low variation across binding energies supporting the stable interaction of VADRPA01 with the 5J2T protein. Analysis indicates that binding is predominantly driven by van der Waals and electrostatic interactions, countering positive contributions from solvation energies. Furthermore, minimal standard error of the mean (SEM) values affirms the reliability of the estimated binding energies. Further comparison of solvation-free energy (ΔGSOLV) values between

VADRPA01 and the native complex Vinblastine (VLB) reveals that the new derivative exhibits a more favourable ΔGSOLV (1003.33 kcal/mol vs. Vinblastine's 886.48 kcal/mol), suggesting an enhanced solvation effect, which is consistent with prior findings showing that VADRPA01 has a higher solubility than Vinblastine. Despite a slightly reduced total binding affinity, the findings reinforce the reliability of VADRPA01's stability, confirming that it remains a strong candidate for additional study. The gmxMMPBSA analysis, illustrated in Figure 07, breaks down the energetic components of the binding interaction, revealing that VADRPA01's binding to 5J2T is primarily stabilized by electrostatic forces (EEL) and van der Waals interactions (VDWAALS). These forces play a central role in the ligand's stable binding with the protein's tubulin structure. Additionally, solvation energy (GSOLV), particularly the electrostatic component (EGB), significantly to stabilize the VADRPA01-5J2T complex. This component's crucial role reflects the extent of solvation's influence on the binding interaction.

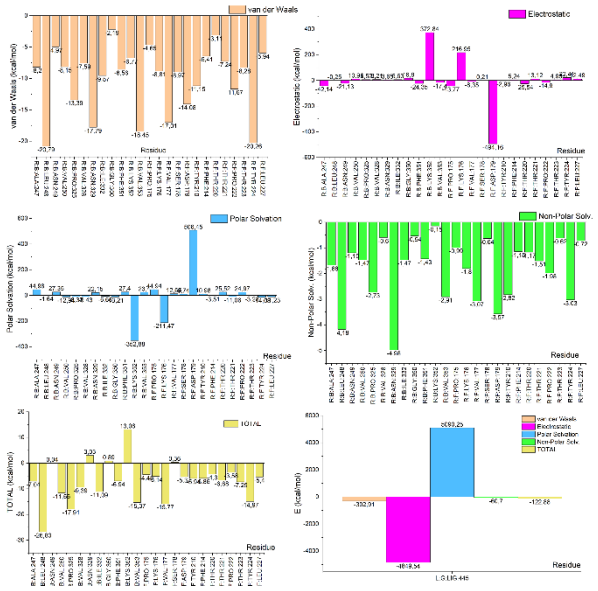
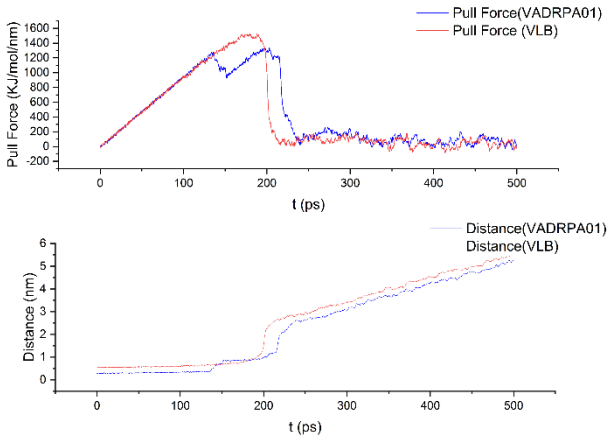


Figure 07. Shows the individual residues energy fluctuations during the MD simulation. ASN249, ASN329, GLY350, and SER178 shows positive delta total energy values while majority of the residues making contact with the ligand shows favourable energy levels. Among them VAL177, VAL353, PRO325, LEU248, ILE323 and THY224 are showed -15,77, -15.37, -26,83, -11.09, -14,97 kcal/mol respectively

The per-residue decomposition analysis identifies key residues, such as for instance, residues such as B: ALA:247, B: LEU:248, and B:PRO:325 as major contributors to binding energy, implying that these residues are essential to maintaining the stability of the complex. Heatmap visualizations of energy contributions reveal that certain residues consistently support stability across the simulation frames, with residues such as B: LEU:248 and B: VAL:353 standing out as critical for sustaining the complex structure.

These stable contributions indicate minimal conformational changes or instability, reinforcing the protein-ligand complex's robustness over time.

Additionally, the study incorporates umbrella sampling to provide more granular insights into protein-ligand stability. This method, which computes free energy profiles for ligand binding, is invaluable for assessing binding stability under varied conditions. The umbrella sampling results, in Figure 08, depict the pulling force changes along the z-axis during a 500-ps simulation. Both VADRPA01 and VLB initially exhibit a rapid escalation in pulling force, peaking before gradually decreasing. The peak force is slightly



higher for VADRPA01 than Vinblastine, suggesting a marginally stronger interaction with the protein.

Figure 08. Pull force distribution during the dissociation of the VADRAPA01 and VLB native complex with 5J2T Tubulin molecule

The force profile indicates that at around 200 ps, a significant drop in force occurs, signalling the ligands' dissociation from the binding site. Post-200 ps, force levels remain substantially lower, highlighting the initial binding strength of the ligands. This peak force correlates with the interaction strength, reinforcing that VADRPA01 may exhibit somewhat stronger binding interactions with the 5J2T protein before fully dissociating. The distance plot further illustrates that both ligands maintain proximity to the protein for similar durations, but VADRPA01's slightly elevated peak force implies stronger interactions before separation.

In conclusion, the binding analysis of VADRPA01 with 5J2T demonstrates that the DIMD protocol effectively generates stable binding poses for this derivative in the tubulin complex. The gmxMMPBSA results reveal favorable binding energies, dominated by van der Waals and electrostatic interactions, with the essential contributions of specific residues identified through decomposition analysis. Stable per-residue energy contributions affirm the complex's resilience, while solvation energy and electrostatic forces stabilize the

interaction. Umbrella sampling further supports these findings by illustrating the force profile during ligand dissociation, where VADRPA01 exhibits stronger initial binding interactions than the native VLB complex.

This comprehensive analysis reveals that the optimized VADRPA01-5J2T complex has a high potential for further experimental and computational study. The combined methods, gmxMMPBSA, decomposition analysis, and umbrella sampling provide in-depth insights into the stability and interaction dynamics of VADRPA01 binding with 5J2T, establishing a foundation for developing effective novel Vinca derivatives designs using the DIMD protocol.

IV. CONCLUSION

Based on the docking results, it can be concluded that the DIMD procedure significantly enhances docking outcomes compared to the conventional rigid receptor-flexible ligand docking protocol. Specifically, the DIMD method increased the binding affinity of the initial docking by 47.74%, demonstrating its superior efficacy. The incremental improvements afforded by the DIMD procedure have facilitated the identification of the most optimal docking pose for VADRPA01, thereby supporting further drug discovery studies of Vinca derivatives. The conducted molecular dynamics simulations have had a substantial impact on evaluating the docking procedure, underscoring the DIMD method's capability to achieve the best docking poses for molecular docking-based drug discovery studies.

Further future investigation plans could involve mutational analysis of the identified key residues to validate their contributions to the binding. Additionally, extending the simulation time and exploring different conformational states of the protein could provide a more comprehensive understanding of the binding dynamics and stability.

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AUTHOR BIOGRAPHY

H.M.A.J. Halahakoon has been serving as a Lecturer in the Department of Pharmacy, Faculty of Allied Health Sciences at General Sir John Kotelawala Defence University since 2020. Prior to this academic role, he gained industry experience as a Research and Development Scientist in the pharmaceutical sector. His research interests include nanotechnology-based drug delivery systems, computational drug discovery, and the development of pharmaceutical dosage formulations.

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