A critical review of mathematical models for combination cancer therapy

Kevin Bosire Basita (kevinb@aims.ac.za)
African Institute for Mathematical Sciences (AIMS)

Supervised by: Dr Joseph Malinzi
Department of Mathematics University of Eswatini, Kwaluseni, Swaziland.

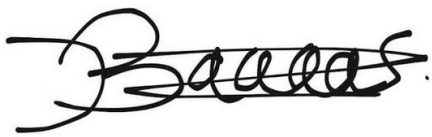
23 May 2019
Submitted in partial fulfillment of a structured masters degree at AIMS South Africa

Abstract

The long-term efficacy of targeted therapeutics for cancer treatment is significantly limited by drug resistance. Experimental studies indicate that among the factors enhancing the rapid acquisition of drug resistance are included inherent cell heterogeneity, microenvironment adaptations to targeted therapy, drug efflux and cell death inhibition. Combinatorial treatment regimens often demonstrate diverse modes of action and thus many times constitute a promising approach to overcome drug resistance. Due to the cost involved in clinical experimentation, mathematical models have shown the potential to aid in discovering rationable combinations for cancer treatment. The understanding of the evolution of cancer combination treatment models and their diverse mechanisms is subject to the development in mathematical analysis and modelling. In this review, we analyse mathematical models on combination cancer therapy thus far developed on various combination regimens and highlight the open questions that are yet to be addressed. Comparisons of the plausible combinations are discussed and the best among them is given based on the impact on toxicity, drug resistance, survival benefits, preclinical trials and side effects. In the end, open problems still in existence and future directions are given.

Declaration

I, the undersigned, hereby declare that the work contained in this research project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.



Kevin Bosire BASITA, 23 May 2019

Contents

1. Introduction

1.1 Background of the Study

Cancer is regarded as one of the most intricate diseases with prominent causes of mortality and one whose treatment remains burdensome in medical care. Cancer treatment in recent years has heavily relied on chemotherapy, radiotherapy and surgical intervention with surgery remaining the main cancer treatment modality where the bulk of the tumours are surgically removed, Hu et al. (2016). But due to its inability to access peripheral parts, surgery-induced tumour acceleration and subsequent metastatic growth have rendered it as ineffective. Chemotherapy and radiotherapy, on the other hand, provides a pertinent supplementary treatment with their efficacy arguably far from convincing mainly because of the drug delivery problems as well as drug resistance, Hu et al. (2016). Besides, traditional monotherapies are known to induce toxicity, are unable to distinguish tumour cells from normal cells and causes adverse side effects to the patients.

Owing to the physiological complexity of the tumour, no single therapy or stand-alone therapy could be able to produce sufficient results for cancer treatment, Hu et al. (2016). However, cancer drugs have been proved to be more effective when administered in combination. The logic behind effective combination therapy is to utilize drugs that use different mechanisms of action, thereby reducing the possibility of resistant cancer cells developing. Combining drugs that have different effects ensures that the optimal dose of each of these drugs is used without intolerable side effects. Combination therapy is essential to advanced cancers where traditional therapies such as radiation therapy or surgery are not suitable, for instance, people with bladder cancer or non–small cell lung cancer that cannot be absolutely removed by surgery. The type of cancer and the stage it is in generally dictates on whether single therapy or combination therapy will be used. Cancers that are locally confined can be treated by surgery or radiation therapy but in some cases radiotherapy can be used before or after surgery to reduce a tumour, thereby increasing chances of complete surgical removal and destruction of the residual cancer cells.

Combination cancer treatment targeting cancer inducing cells or cell sustaining pathways is presently considered a keystone of cancer therapy, Mokhtari et al. (2017). Although mono-therapeutic approach claims a large share in the medical set-up for the treatment of different forms of cancer, it's considered less effective in comparison with the combination therapy approach, Ottolino-Perry et al. (2010). Standard mono-therapeutic techniques destroy all the actively proliferating cells non-selectively, ultimately causing the annihilation of both healthy and cancerous cells, Ottolino-Perry et al. (2010). Chemotherapy is known to produce toxic effects on the patients with myriad side effects and threat to life, and can greatly affect bone marrow cells and increase susceptibility to host diseases, Ottolino-Perry et al. (2010).

By targeting different pathways, combination therapy significantly lessens the toxicity of the single therapeutic agents. Combination cancer treatment therapies hold great appeal in boosting the efficacy of anticancer drugs, enhancing apoptosis, suppressing tumour growth and decreasing cancer stem cell population, Malinzi (2019). Further, combination treatment modality reduces significantly incidences of drug resistance. Although amalgamation therapy could be toxic if it involves chemotherapeutic agents, toxicity is greatly reduced because different pathways will be targeted, (Mokhtari et al. (2017), Malinzi (2019)). Moreover, this works in an additive manner, thereby lowering the amount of therapeutic dosage needed in each individual drug, Mokhtari et al. (2017) Additionally, combination therapy could prevent toxicity on normal cells while simultaneously producing cytotoxic effects on cancer cells, (Mokhtari et al. (2017), Malinzi (2019)).

Its generally agreed that cancer is a result of the combination of interconnected disease pathways that are incapable of being treated effectively by a single therapeutic agent or strategy, Hu et al. (2016). Several advances have been made in tumour profiling and deep sequencing, revealing driver mutations as well as yielding novel targets for the inception of new cancer drugs, Dry et al. (2016). In spite of the progress in determining and diagnosing genetically defined tumour subgroups and the patients most likely to benefit from available treatments, these therapeutic agents are yet to establish their full potential, partly because of the intrinsic and adaptive resistance of tumours, Dry et al. (2016).

Much attention has been laid to amalgamations resolving to promote the death of tumour cell and objective responses despite tumours being under the influence of numerous components of their microenvironment and patient response being influenced, on a broader basis, by components of overall health, Dry et al. (2016). The inability of preclinical models to recapitulate all aspects of tumour and patient biology limits their application severely, Dry et al. (2016).

There have been remarkable achievements on the combination therapy in recent years with much attention focussing on most effective combinations that are likely to produce significant effects on the tumour. However, this journey has not been smooth with the process of coming up with plausible combinations facing numerous challenges. Current combination cancer therapy presumes that better results are obtained by amalgamating therapeutic drugs at their maximal tolerated doses, Lopez and Banerji (2017). Nevertheless, differences in the pharmacokinetics of single drugs bring about inconsistency in the delivery of synergistic drug ratios to tumour cells. What is more, compounded toxicity observed in combination treatment protocols calls for application of suboptimal dosages to counter the effects. Additionally, there are also challenges regarding the identification of best drug combinations, best combination strategies and the complications involved in the combination therapy, Lopez and Banerji (2017).

Upon the selection of a reasonably designed combination, the process of its early clinical development is complicated requiring attention to detail, Lopez and Banerji (2017). Implementation of combination strategies is influenced by several issues including toxicity, pharmacokinetic and pharmacodynamic interactions, proper timing of the resistance development and the identification of robust biomarker in predicting the response. Clearly, the questions of how to implement the combination, when to implement the combination and to whom its implemented for are the major problem that faces clinical community during the test of a drug combination, Lopez and Banerji (2017). Most often drugs used in combination regimen is already approved by Food and Drug Administration (FDA), cutting the costs of combination therapy research and thus increasing the cost efficiency of therapy consequently easing off the burden of the medically disadvantaged patients, Mokhtari et al. (2017).

Cancer is a multiplex disease involving diverse interplays of molecules leading to robust, redundant and compensatory networks, Jeon et al. (2018). Treatment of cancer with a single drug targeting a particular molecule necessitates cancer to discover bypasses in the networks and discover other cancer addicted pathways in order to circumvent apoptosis or proliferation, Jeon et al. (2018). This makes it hard in an attempt to develop a sustainable targeted cancer drug. Since the 1960s which saw MOPP (Mechlorethamine, Oncovin, Procarbazine, Prednisone) used for the treatment of Hodgkin's lymphoma, a lot of drug combination therapies have been approved by FDA, currently standing at more than 50, Jeon et al. (2018). Moreover, it is not always the case that drug combination therapy will be better than a single drug treatment as it is possible to have synergistic or antagonistic effects on the account of genetic difference of a person. This genetic variation makes it hard to come up with biological hypotheses and experimentally determine effective drug combinations, Jeon et al. (2018).

For this reason, efficient mathematical approaches are needed to try and understand different mechanisms of cancer activities at a relatively less cost. Many Mathematical models have been formulated

to determine effective drug combination therapies for cancer treatment. Although many mathematical models have been developed, the cure for cancer is still far from reach, with complexities associated with therapeutic combinations hampering their clinical use. Over the past few years, much attention has been shifted to diagnosis, modelling and cancer treatment not only in the biological and clinical researchers but also in the scientist community, Ghaffari et al. (2016). A mathematical model is known to provide appropriate contexts in answering pestering questions concerning the behaviour of immune cells in the presence of cancer cells and how the tumour cell behaves in the presence of drugs, Ghaffari et al. (2016). Production of new anticancer drugs takes a long time and medical examination is costly and risky and thus a suitable mathematical model and appropriate control model for the infusion of drugs is needed. Mathematical models play a pertinent role in analysing the efficacy of new drugs thus reducing many of these problems and this is good news to the clinicians and medical world at large as they would be able to predict and control the behaviour of cancerous tumours, Salari et al. (2015).

1.2 Problem Statement

Combination cancer drug therapy, regarded as a substitute for single cancer drug therapy, in the recent years has gained a lot of attention in the research arena and has been shown to potentially mitigate resistance and toxicity in addition to boosting synergistic efficacy. Despite the promising results in improving the overall survival of cancer patients, implementation and testing of a drug combination therapy are laborious, requiring attention to details at least in the early stage of clinical trials. Many Mathematical models have been formulated to determine effective drug combination therapies for cancer treatment. Although many mathematical models have been developed, the cure for cancer is still far from reach, with complexities associated with therapeutic combinations hampering their clinical use. A mathematical model is known to provide appropriate contexts in answering pestering questions concerning the behaviour of immune cells in the presence of cancer cells and how the tumour cell behaves in the presence of drugs. Production of new anticancer drugs takes a long time and medical examination is costly and risky and thus a suitable mathematical model and appropriate control model for the infusion of drugs is needed.

1.3 Aims and Objectives of the Study

The main aim of this project is to carry out a critical review of mathematical models for combination cancer therapy. The objectives of the study are: to discuss the different cancer treatment types and review existing mathematical models of combination cancer therapy. Existing open problems are identified and we propose plausible combination protocols for cancer treatment.

1.4 Tradtional Cancer Therapies

A variety of cancer treatment therapies such as chemotherapy, surgery and radiotherapy have been used as cancer treatment protocols over the past few decades. Advancement in technology led to the improvement and incorporation of new forms of cancer treatment modalities including targeted therapy, immunotherapy and oncolytic virotherapy.

1.4.1 Chemotherapy. Chemotherapy involves using anti-cancer drugs to combat cancer by killing cancer cells. Chemotherapeutic agents are broadly categorized into targeted drugs which entails interfering with cancer-specific pathways and cytotoxic drugs which works by targeting rapidly replicating cells thereby killing targeted cells by stopping cell division and ensuring the destruction of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), Mahasa (2017). Chemotherapy can be administered orally, through intravenous injection (injection into the bloodstream), through intra-arterial and intravenous infusion so as to directly destroy tumour cells, Malinzi (2015). Chemotherapeutic drugs suppress the cells thereby stopping or reducing the rate at which they divide and multiply. Chemotherapy can be administered with a curative intent i.e in combination with other drugs or palliatively. A major challenge that chemotherapeutic drugs pose is their inability to distinguish between rapidly replicating cancerous and healthy cells, (Mahasa (2017), Malinzi (2015), Mokhtari et al. (2017)). It is stipulated in Mahasa (2017), that some non-cancerous cells, for instance, immune cells are known to replicate rapidly and such cells are altogether exterminated by chemotherapeutic drugs. Chemotherapy varies from patient to patient and is administered depending on the type of cancer and its stage (how far it has advanced). Chemotherapy causes adverse effects including nausea, vomiting, diarrhoea, loss of appetite, and loss of hair which would impact the quality of life, increasing frequency of hospitalization, and emergency department visits, Chan et al. (2016).

1.4.2 Radiotherapy. Radiotherapy entails using high-energy rays which pierce tumour host tissue thereby shrinking and killing tumour cells. High dosage of energy rays annihilates the DNA of cancer cells thus hampering their division and eventually lysing them out, Baskar et al. (2012). Radiotherapy may cure various types of cancer when it's localized in a specific part of the body. Radiation therapy can function as adjuvant therapy in order to prevent the recurrence of cancer after surgery has been performed to remove original malignant or it can be used as part of neoadjuvant therapy which entails application of therapeutic agents before main treatment begins. Since radiation passes through the skin and some organs, ensuring the safety of normal cell involves applying radiation at various angular positions (shaped radiation) and ensuring the angles intersect at the tumour thereby causing high absorbed rates as compared to the adjacent healthy cells.

Radiation oncologist prescribes the radiation with the intention of curing. Radiation may also be used in adjuvant therapy and in palliative treatment, Baskar et al. (2012). It's a common practice to synergize radiotherapy with other types of treatment such as immunotherapy and chemotherapy, Chan et al. (2016). Application of accurate treatment intent is subject to the type of tumour, where its located, the stage it is in and the health condition of the patient. Various types of cancer show a varied response to radiotherapy. How particular cancers respond to radiation can be explained by radiosensitivity where highly radiosensitive tumours are quickly destroyed by a modest dosage of radiation. Some cancer requires high energy to achieve radial cure while others like melanoma are notably radioresistant. A computerized tomography (CT) scan is commonly done before treatment so as to identify cancer and the neighbouring normal structures. Radiotherapy causes side effects which include nausea and vomiting, intestinal discomfort, infertility, epilation (hair loss) and swelling.

1.4.3 Targeted therapy. Targeted therapy is a form of pharmacotherapy which instead of meddling with health cells operates by obstructing massive growing of cancer cells with the aim of interrupting specific targeted molecules that are responsible carcinogenesis and tumorigenesis. The first ever targeted therapy was tamoxifen and was approved in 1970s. Tamoxifen is attached to the estrogen receptor (ER), preventing estrogen from binding to ER thereby modulating ER activity, Yan et al. (2011). Targeted therapy uses biopharmaceuticals and as such sometimes biologic therapy is synonymously used to mean Targeted therapy to distinguish it from chemotherapy. Targeted therapy can also use nanoengineered enzymes so as to affix into the tumour cell. It's expected that this kind of treatment should be efficacious

and thus doing less damage to the normal cells. Targeted therapies employing chemical entities targeting protein or enzyme mutagens has been considered as the most successful. There are different targeted therapies for various forms of cancer such as melanoma, breast cancer and lymphoma.

1.4.4 Precision medicine. This is an approach to patient care that allows doctors to select treatments that are most likely to aid patients on the account of a genetic understanding of their disease. The idea of precision medicine is not new, but recent advances in science and technology have helped speed up the pace of this area of research, National Cancer Institute. Precision medicine (PM) involves prevention and treatment that takes into account each person's variability. PM has been greatly improved with immense biologic databases set up and powerful tools put in place to aid in the classification of individuals. This form of treatment rests upon the availability of biological makers which entail an evaluation of normal biological and pathogenic processes as well as pharmacological responses to treatment interventions. It is important to know who benefits most out of this targeted treatment and harmonize treatment decisions through merging of information obtained from genomics, blood biomarkers, imaging, and data collected from proteomics.

1.4.5 Immunotherapy. Recent studies have seen an increasing desire to decipher the functionality of the immune system in response to the presence of foreign cells. Immunotherapy can be described as a form of treatment modality that induces or boosts a person's immune system with a view to combating tumours or cancer, Page (2009). Immunotherapy takes advantage of the fact that cancer cells always have tumour antigens that could be spotted by antibody protein. During the process of immune surveillance in the body cells, the host develops some defence mechanism to help fight the unknown antigens. Immunotherapy involves the use of vaccines, the use of monoclonal antibodies and the use of immunity strengthening substances , Malinzi (2015).

The use of immunity strengthening substances involves injecting non-specific immunotherapies into the body so as to boost the immune system. Monoclonal antibodies have shown effective results as cancer therapeutics when a specific target was focused on surface antigens located in tumour cells. Examples of monoclonal antibodies that are currently in use include Nivolumab, Bevacizumab, and Brentuximab vedotin, Malinzi (2015). Usage of antibodies to obstruct paths hindering internal or endogenous immune response against cancerous tumours, referred to as checkpoint blockade therapy has elicited excitement in the scientific community and patients alike. Normal antibodies get affixed to exogenous pathogens whereas the 'manipulated immunotherapy' antigens get attached to cancerous antigens thereby staining cancerous cells and making it easy for immunity to suppress or kill them. Vaccines used involves either treatment vaccines which helps the body's immunity to kill cancer cells or preventive vaccines given to an individual without any cancer signs in order to inhibit the development of specific cancers. For a more succinct review on immunotherapy see Galluzzi et al. (2014). The side effects associated with immunotherapy include fatigue, rashes, fever and nausea.

1.4.6 Hormonal therapy. Hormonal therapy (HT) entails estrogen therapy (ET) and estrogen-progestogen therapy (EPT) when outcomes are not specific to one or the other treatment. Hormone therapy is a cancer treatment that slows or stops the growth of cancer that uses hormones to grow, National Cancer Institute. Hormonal therapy is where specific hormones such as steroid hormones or drugs with inhibitory characteristics are exogenously administered to alter or manipulate the endocrine system. One of the most important characteristics of steroid hormones is the gene expression in some cancer cell and thus altering the way they operate can result in some of the cancers ceasing to grow or dying. Hormonal therapy also employs orchiectomy and oophorectomy to surgically remove some of the endocrine organs. HT can be used in various forms of cancers including the breast and prostate cancers. One of the mostly used Hormonal therapy in oncology is tamoxifen for remedying breast cancer although now aromatase inhibitors such as letrozole and anastrozole are taking over due to their expanding role in the disease

for example in postmenopausal women for the treatment of breast cancer.

1.4.7 Oncolytic virotherapy (OVT). Oncolytic virotherapy is a treatment modality that entails genetic manipulation of organisms (Viruses) with the properties of infecting, self-replication and lysing cancer cells with little or no harm to normal cells, Galluzzi et al. (2014). The tumour specific properties of oncolytic viruses guarantee them viral binding, entry, and replication. Oncolytic viruses (OVs) can be categorized into those with a natural tumour tropism and those that are genetically engineered to target tumour cells, Galluzzi et al. (2014). The viruses multiply by seizing the genomic composition of the host cells. The viruses and their progenies can leave the body through the viral apoptosis, budding and exocytosis. OVT works by unanimously corrupting and killing cancer stem cells (CSCs). Oncolytic viruses (OV) can be administered either through intratumoral(direct injection into the tumour) or by intravenous injection (injected into the bloodstream). Intravenous injection of OVs has shown improved results as a treatment option for metastatic tumours, Galluzzi et al. (2014).

Oncolytic viruses do not undergo replication in normal cells as opposed to in cancer cells majorly due to the absence of DNA replication region in normal cells. OVs ability to trigger the host's immune response ensures that oncolytic viruses undergo lysis thus producing viral cells that attack more cancer cells. However, an infection of OVs leads to a change in the already established immunosuppressive microenvironment. The self-immolation of cancer cells occurs heightened by the OVs ability to induce immunogenicity within CSCs. In fact, it was initially thought that teaming up the immune system with OVs would negatively impact the immune system and thus lead the body to develop defence mechanisms against the virus. But on the contrary, OVs stimulates the development of immunogenicity triggering antigens to launch an assail on cancer. Examples of oncolytic viruses that have been approved by the FDA include T-VEC with others currently being in their phase II/III of clinical trials, Galluzzi et al. (2014).

1.5 Combination Therapy

Combination therapy first surfaced in 1965 when pedriatic patients with acute lymphocytic leukaemia received a combination treatment of methotrexate, 6-mercaptopurine, vincristine and prednisone, where it was confirmed successful in lessening tumour burden and prolonging remission, Mokhtari et al. (2017). As a result of the success of these combinations of drugs in treating acute lymphocytic leukaemia, research in cancer therapy gained an enormous amount of attention focussing on the combination therapies targeting different pathways in a characteristically synergistic manner, Mokhtari et al. (2017). Currently, much of the focus is laid in combining treatment modalities that act in a synergistic manner in combating the dreadful disease. This approach has been reported to have shown improved results in cancer treatment. These improved results due to the amalgamation of cancer therapies can be attributed to reduced drug resistance, reduction in CSCs population, killing of cancer cells, the potential reduction in metastasis amongst others Mokhtari et al. (2017). In this study, we present some insight into different forms of cancer combination treatments which should be rationally considered for further development. A detailed discussion of these combinations is given below.

1.5.1 OVs combined with external beam radiotherapy. The combination of OVs with radiation through tumour sensitization and radiation-mediated enhancement has been shown to bring about synergistic antitumoral effects in a number of preclinical models. For example, adenovirus such as ONYX-015 and Ad$\Delta 24$ in combination with radiotherapy resulted in about 50 -100 % likelihood of survival in a subcutaneous glioma model, Ottolino-Perry et al. (2010). However, on the contrary, some combinations with other viruses, for example, AdΔ24RGD recorded no significant improvement on the

antitumor effects in an orthotopic glioma model. Of interest is the synergistic inhibition on prostate cancer resulting from the combination of adenovirus CV706 with external beam radiotherapy, Ottolino-Perry et al. (2010)

Oncolytic virotherapy of Herpes simplex virus (HSV) in combination with external beam radiotherapy recorded a significant improvement on the outcomes of some cancer, Ottolino-Perry et al. (2010). In an attempt to find the relationship of NV1023 in conjunction with external beam radiotherapy 3 models of cholangiocarcinoma were used to study the outcomes. A reduced tumour volume was observed in one model (where 2 different doses of the virus were administered) while the other two models recorded no difference when compared to individual therapies.

1.5.2 Chemovirotherapy. Chemovirotherapy is the combination of treatment therapies of chemotherapy and virotherapy, Malinzi et al. (2017). OVT has attracted many researchers in recent years but despite this widespread fame, virotherapy has been shown to have limited applications mainly because of their continued usage as monotherapeutic modality and hence nothing really significant has been achieved clinically. However, a combination of OVT with chemotherapy has been known to produce quick stabilization and thus creating more time for immunotherapeutic achievement. Combination treatment regimen has many benefits as it permits dose reduction, produces synergistic interactions and reduces cell- drug resistance among other benefits. Current clinical evidence suggests that this amalgamation (OVT with Chemotherapy) could be the key to unravelling full potential of virotherapy while at the same time suppressing induction of resistance, Mokhtari et al. (2017).

The success of chemovirotherapy is subject to tumour masses being low before application of virotherapy and ability to curb abnormal growth of tumour before treatment. Continuous combinations of different OVs with chemotherapy has been proven to be very expensive both in time and money in a clinical setting thus what remains to be seen is how to balance clinical chemovirotherapeutic regimens with systematic testing, how to monitor the progress and how to optimize the outcomes from various combinations. Each combination has to undergo clinical phases I, II and III with phase I or II concerned in maintaining balance beneficial and deadly effects on immunity and multiplication of virotherapeutics. Nonetheless, this combination produces toxicity to body cells and the problem of distinguishing which of the two-chemotherapy or virotherapy induces the toxicity.

1.5.3 Oncolytic virotherapy in combination with targeted radionuclide therapy. Targeted radionuclide therapy is suitable for administration on subsets of cancers that over-express specific receptors. For example, thyroid tumour which is known to bespeak sodium iodide symporter (NIS) and somatostatin are treated by Radiolabeled iodine, Ottolino-Perry et al. (2010). One of the disadvantages that targeted radiotherapy has faced is its limitation with receptor-positive tumours. Nevertheless, with the advancement in research, it has been found that OV makes targeted radiotherapy achievable regardless of their endogenous receptor status making it possible for the detrimental rays to assault the infected cells. During this process, the normal cells are able to evade the sustained collateral destruction which might have occurred in the process of radiation, Touchefeu et al. (2012).

Numerous studies have been carried out in relation to designing and encoding the hNIS gene. One of the oncolytic viruses that have been studied is an adenovirus Ad-yCD/mutTKSR39rep-hNIS which resulted in accumulation of ^{99m}Tc in a sarcoma model, Ottolino-Perry et al. (2010). It was demonstrated that amalgamating vesicular stomatitis virus (VSV) (known for its inability to the production of interferon (IFN)) and NIS (VSV(51)-NIS) expressed with radiotherapy extended the possibility of survival at least relative to the virus in a multi myeloma model, Ottolino-Perry et al. (2010). Despite this success, there is still a lot to be done in order to determine the efficacy of this combined treatment modality.

1.5.4 Combination of viruses. It has been suggested OVs should be combined with other viruses. For instance, in the event that immune response to one virus crops up, then it may be a brilliant idea to use another virus as a supplement to continue with treatment. Practically, the implementation of this has been considered as nearly 'improbable' in a clinical setting. However, in a study by, Ottolino-Perry et al. (2010), it was established that the immune evasion of genes vaccinia virus (VV) make cells develop some resistant to decimation by VSV. In this case, VV acts as a suppressant of the inbred antiviral immune system, allowing VSV to corrupt, infect and destroy the tumour related cells.

1.5.5 Immunovirotherapies. OVs are novel anticancer treatment currently being investigated in the clinical setting. The need for improved cancer treatment in modern society has necessitated the emergence of new cancer treatment modalities in recent years. One such outstanding breakthrough entails the amalgamation of virotherapy and immunotherapy to combat cancer. Most studies have been focused on understanding the properties and modes of action of these viruses and their antitumour effects, and it has been shown that OVs offers a promising future upon the combination with immunotherapy in addition to combining with other existing treatment modalities, Jenner et al. (2018). Intratumoral injections of OVs initiates a reaction in the host's immune system leading to the invasion of tumour site by immune cells. Amalgamating OVs with immunostimulatory cytokines initiates an additional antitumour immune response with apoptosis of normal and infected tumour cells occurring due to suppressive properties of immune cells, Jenner et al. (2018). During replication in the tumour, OVs produces pathogens that are responsible for instigating as well as enhancing antitumor immunity. These pathogens supply cancer antigens to dendritic cells through oncolysis while concurrently giving " lethal signals" vital in promoting localized inflammation and activation of dendritic cells.

1.5.6 Chemoimmunotherapy. Chemoimmunotherapy involves the combination of chemotherapy and immunotherapy modalities of treatment. The combination of chemoimmunotherapy has been studied since the 1990s to understand their modes of action as each modality has different mechanisms of action, Medina-Echeverz and Berraondo (2012). This has led new therapeutic interventions based on boosting the host's immunity to fight against cancer. Clinical and preclinical experiments back the idea of remodelling the tumour microenvironment in order to alter the innate and adaptive inhibition responses emanating from the tumour towards developing antitumour immunity. For example, oxaliplatin has been shown to clinically induce tumour cell death in colorectal cancer with the likelihood of stimulating immune responses termed as immunogenetic cell death, Medina-Echeverz and Berraondo (2012).

Preclinical and clinical settings have recorded numerous immunotherapeutic approaches with the goal of battling carcinoma have been tested so far. Clinical trials including the amalgamation of chemotherapy of oxaliplatin (FOLFOX), 5-fluorouracil, cytokines IL-2 and folinic acid with EGF receptor or VEGF have been preferably used as chemotherapeutic treatment regimens, Medina-Echeverz and Berraondo (2012). Chemoradiotherapy (CRT) Chemoradiotherapy also called chemoradiation involves administering several chemotherapeutic agents alongside radiation to enhance the destruction of a tumour cell. Chemoradiotherapy is categorized into neoadjuvant, concurrent, or adjuvant on the account that chemotherapy drugs are administered before, during, or after the course of radiotherapy, Salari et al. (2015). Clinically, It has been proven that concurrent CRT results in better control of local tumour for many treatment sites compared to radiotherapy. The rationale of amalgamating chemotherapy with radiation varies greatly in concurrent CRT. Nevertheless, Steel and Peckham (1979) proposed the grounds for combining two modalities: spatial cooperation, additivity, radio-sensitization and radioprotection. Local tumour control Enhancement is better described by the mechanisms of additivity and radio-sensitization.

1.5.7 Chemoradiotherapy. The spectrum of modern medicine is continuously increasing with the early 1940s focussing on chemotherapy, 1990s concentrating on targeted therapy and immunotherapy, and early 20th-century seeing surgery and radiotherapy as the mainstays of treatment, Grassberger

and Paganetti (2016). The paradigm of the interplay between radiation and chemotherapy was first conceptualized by Steel and Peckham in 1979 and was later summarized by, Seiwert et al in 2007 Grassberger and Paganetti (2016). The cooperation between chemotherapy and radiotherapy can be categorized as a spatial corporation where there is no interaction between the two modalities and in-field cooperation where the two modalities contribute to loco-region control. Radiation restricted to a small field-size and thus it is more effective in the elimination of local diseases. Two of the fundamental reasons why combination therapy should be used assuming there is no interaction between the two modalities is to be able to use cytotoxic drugs that will be used to tackle the disease, not within the radiation field and to irradiate seclusion sites in regard to eradicating the disease thwarting the success of chemotherapy, Steel and Peckham (1979). Radiotherapy and cytotoxic agents can either be concurrently or adjuvant/neo-adjuvant, that is, with chemotherapy treatment following/ preceding radiotherapy.

1.5.8 Radioimmunotherapy. Radioimmunotherapy (RIT) is the amalgamation of radiotherapy and immunotherapy particularly used to treat non-Hodgkin B-cell lymphoma and other forms of cancer. RIT uses engineered monoclonal antibodies paired with radioactive materials called radiotracers, Jenner et al. (2018). When injected into the patient's bloodstream, they bind to cancer cells and deliver a high dose of radiation directly to the tumour. The amalgamation of immunotherapy with radiotherapy is done using different modalities, thus it is critical to determine the association of the exact scheduling of radioimmunotherapy. Combining radiotherapy with immune checkpoint blockade may offer considerable therapeutic impact if the immunosuppressive nature of the tumour microenvironment (TME) can be relieved. Radioimmunotherapy first occurred with haematological malignancies where ^{131}I-labelled anti-HLA-DR antibody achieved a significant bulky masses regression, particularly with Non-Hodgkin Lymphoma (NHL), Sharkey and Goldenberg (2011). Despite a reported success in the subsequent trials with various antibodies in lymphoma, RIT was inhibited by haematological toxicity since radiolabeled antibody disappeared steadily from the blood, subjecting the radiosensitive bone marrow to a perpetual low-dose irradiation, Sharkey and Goldenberg (2011). A number of issues have hampered the acceptance of radioimmunotherapy, for example, the cases of secondary cancers and myelodysplastic syndrome (MDS) is a worry, but evidence suggests the overall risk associated with RIT is less than chemotherapy, Sharkey and Goldenberg (2011). RIT of the solid tumour remains a challenge with the obvious issues being that most of the antibodies used unable to affect tumour, Sharkey and Goldenberg (2011).

2. Review of mathematical models for combination cancer therapy

The process of cancer treatment has been modelled for a long time by focussing on different aspects of cancer development. In recent times, the focus has been placed in modelling combination therapies since they have shown some promise in the treatment of cancer. This review looks into the mathematical models that have thus far been developed in various combination regimens, bearing in mind that these are not the only combinations in existence today.

2.1 Models of Chemoimmunotherapy

Recent years have seen chemoimmunotherapy gain fame in the research community due to the current trend of its continuous application in practical sense, Rodrigues et al. (2019). Therapeutic cancer vaccines and cancer-specific immune cells are currently under study and have shown promising hopes in fighting against the negative impacts of chemotherapy. Nonetheless, there are many questions whose answers are yet to be found, for instance, how the immune system interplays with a tumour and what elements in the immune system have a crucial role in responding to immunotherapy. In this respect, several mathematical models have been developed in an attempt to model immune response dynamics under chemoimmunotherapy.

Modern cancer treatment methods rely on the ability of certain cancers to trigger the immune response. Incorporation of the immune component in the formulation of mathematical models has played a key role in the clinically observed phenomena, for instance, tumour dormancy, unchecked growth of tumours and oscillations in tumour size, Isaeva and Osipov (2009). The first attempt to illustrate the immunotherapy related effects in a suitable ODE model was given by Kirschner and Panetta (1998). The study utilized IL-2 along with adoptive cellular immunotherapy (ACI) by developing dynamical equations explaining external inflow of both IL-2 and cultured immune cell.

Chappell et al. (2015) stipulated that despite much research being devoted to understanding tumour-immune interactions, there still exists open question in the field. They presented a high-level abstraction mathematical model that explored the interaction of immune cells and tumour cells, and they further explored the merits of amalgamating immuno-oncology agents with chemotherapy and radiotherapy. The underlying assumption was that there does not exist mass transfer resistance. The model was tested and numerical simulations were done by using data similar to that shown in Deng et al. (2014) but with a slight adjustment in order to produce tumour growth seen in mice without and with treatment. Numerical results showed that tumour mass reduced significantly when radiotherapy and immuno-oncology are used in combination whereas single therapy recorded no significant decrease in tumour mass. Further, a combination of radiotherapy and immuno-oncology leads to an increase in the number of T-cells that are activated compared to single therapies.

It is interesting to mention a paper by de Pillis and Radunskaya (2003) where experimental studies were shown to shed light on the understanding of how a mouse's immunity responds to the tumour. In the study, tumour cells were modified to strengthen their immune stimulating ligands. The experiments conducted showed that high ligand levels create a barrier to the growth of tumour in the mouse. A mathematical model was proposed based on the obtained results from Diefenbach experiments with the aim of answering questions that constantly arise concerning the mechanisms behind immune reactions to

the tumour. The kinetic model of anti-tumour focusing on the interplay between NK and CD8+T cells with different varieties of tumour cells by using a system of ODEs was constructed on the basis of the principle of using the simplest form that would conform to the data. It was shown that ligand transduced cells trigger enough immune response to put tumour growth under control, whereas control-transduced tumour cells evade immunity.

In a more recent study, de Pillis et al. (2009) extended the study to include new interaction terms such as chemotherapy, immunotherapy and vaccine treatments. The model assumed that both the natural killer cells (NK) and CD8+T cells can lyse tumour cells and that in the absence of immunity the tumour follows a logistic growth. The model was analyzed by locating equilibrium points, doing stability analysis, performing a bifurcation analysis and analyzing basins of attraction. Numerical simulations of chemoimmunotherapy and vaccine therapy were presented by using the parameters of both mouse and human. Bifurcation analysis of two systems of parameters indicates that certain values of the parameters can induce a long term behaviour sensitive to the initial conditions. This indicates that if zero and high steady-state points are stable, cells near the boundary dividing the basins of attraction of these equilibria, then minute changes in either the levels of CD8+T or initial size of the tumour can drastically affect the outcome of the disease indicating that chemoimmunotherapy should be employed to restabilize the disease-free state.

A subsequent extension of the above models was done by Rodrigues et al. (2019) in a paper on modelling chronic lymphocytic leukaemia (CLL) where they developed a simple ODE model to determine the dynamics of CLL-immune under the amalgamation of chemotherapy and oncolytic virotherapy. The model considered the interaction of B-lymphocytes and T-lymphocytes and was subjected to several assumptions, for example, cancer cells follow a logistic dynamic growth, cancer cells instigate the production of immune cells, cancer cells and immune cells are identical within a given niche and the elimination of the drug is in accordance with the first order kinetics. Results showed that chemotherapy alone cannot act synergistically with immunotherapy as modes of cancer treatment. It was also established that there is a minimum number of immune cells needed to be transplanted in adoptive treatment so as to ensure there is a complete cure or remission. However, more studies are needed to model chemoimmunotherapy and adoptive cellular immunotherapy.

Collins et al. (2010) in their paper attempted to find the optimal strategy that would help diminish the number of cancerous cells and the quantity of chemotherapeutic drug required in a model that constitutes a nonlinear relationship between cancer cells and immune cells. The existence of an optimal control was established by Pontryagin's Maximum Principle to find the representation of the control through the calculation of the adjoint system that is coupled with the state system. However, more work needs to be done in the numerical aspects of optimal control simulations. However, more work is needed to carefully incorporate delay aspects in the optimal control setting for the forward and backward oriented system in the numerical setting.

The importance of delay of the immune system response was given by Rihan et al. (2014) where Kuznetsov et al's. work was extended to include a delay differential model with optimal control in which they described the interplay of tumour cells, normal cells and immune response cells with external therapy. A DDE model was adopted and analysed with the goal of providing computationally an optimal way of conjoining immunotherapy and chemotherapy treatment strategies that can discern the perfect treatment strategy that minimizes the tumour burden while at the same time maximizing the strength of the immunity. The model gives an account of the response of the effector cells to the growth of tumour cells. It is presumed that all the interplay are in vitro with $E(t), T(t), C(t), E^*(t)$ and $T^*(t)$ representing locally the concentrations of effector cells, tumour cells, effector-tumour cells conjugates,

inactivated effector cells and lethally hit tumour cells, respectively. The model is given below

$$\begin{aligned}
\frac{dE(t)}{dt} &= \sigma + F(C(t),T(t)) - d_1E(t) - k_1E(t)T(t) + (k_{-1}+k_2)C(t),\\
\frac{dT(t)}{dt} &= \alpha T(t)(1-\beta T_{tot}(t)) - k_1E(t)T(t) + (k_1+k_2)C(t),\\
\frac{dC(t)}{dt} &= k_1E(t)T(t) - (k_{-1}+k_2+k_3)C(t),\\
\frac{E^*(t)}{dt} &= k_3C(t) - d_2E^*(t),\\
\frac{dT^*(t)}{dt} &= k_2C(t) - d_3T^*(t),
\end{aligned} \tag{2.1.1}$$

where $F(C(t),T(t))$ denotes accumulation of effector cells in the tumour site , σ is the normal rate at which adult effector cells flow into the tumour side T_{tot} is the total population of the unattacked tumour cells, k_1 and k_{-1} represents, respectively, the rate of binding of effector cells to tumour cells and the rate of separation of effector cells to tumour cells and d_1, d_2 and d_3 represents the rates of elimination E, E^* and T^* respectively. The maximal growth of tumour is given by α and β^{-1} represents the environment capacity. The model also incorporated discrete time delay τ to represent the time needed for the immune system to respond on recognition of the tumour cells. The model incorporating time delay is of the form

$$\begin{aligned}
\frac{dE(t)}{dt} &= \sigma + \frac{\rho(t-\tau)T(t-\tau)}{\eta + T(t-\tau)} - \mu E(t-\tau)T(t-\tau) - \delta E(t),\\
\frac{dT(t)}{dt} &= r_2T(t)(1-\beta T(t)) - nE(t)T(t),
\end{aligned} \tag{2.1.2}$$

where σ is the rate at which effector cells flow into the tumour region, δ is the rate of cell death in the absence of any tumour. The term $\frac{\rho(t-\tau)T(t-\tau)}{\eta+T(t-\tau)}$ represents the stimulation of immune response by the tumour cells with positive constants η and ρ.

The solutions of model (2.1.2) were shown to be nonnegative and bounded. The following proposition was arrived at.

2.1.1 Proposition. Suppose that $L(E,T)$ is the solution of the model (2.1.2); then $E(t) < K_1$ and $T(t) < K_2$ for large time t

where

$$\begin{aligned}
K_1 &= E(0) + \frac{\sigma}{\delta}\exp(\delta t) + \int_0^t \left[\rho e^{\delta(\tau+s)}\left(E(0) + \frac{\sigma}{\delta}e^{\delta_s}\right) \times \exp\left(\int_s^t \rho e^{\delta(\tau+\xi)}d\xi\right)\right] ds\\
K_2 &= \max\left(\frac{1}{\beta}, T(0)\right).
\end{aligned}$$

Considering the system (2.1.1) with $T(t) = T(0)\exp(\int_0^t [r_2(1-\beta T(s)) - E(s)]ds)$ the following result was obtained.

2.1.2 Corollary. Given $\frac{\rho}{\eta+T} \geq \mu$, the solutions of the model (2.1.2) are positive for all nonnegative initial conditions. Nevertheless, if $\frac{\rho}{\eta+T} \leq \mu$, then there are nonnegative initial conditions such that $E(t)$ becomes negative in a finite time limit.

The existence of optimal control problem and optimality system were established with optimal control problem formulated as follows:

$$\max_{x,V} J(x,V) = \psi(x(t_f)) + \int_0^{t_f} L(t,x(t),V(t)dt$$

subject to

$$\begin{aligned} x'(t) &= f(t,x(t),x(t-\tau),v(t), \quad t \in [0,t_f], \\ x(t) &= \phi(t), \quad t \in [-\tau,0] \end{aligned}$$

where J is the objective function and $L(.)$ is the Lagrangian objective function and $V(t)$ is called an admissible control if and only if it fulfils $a \leq v(t) \leq b, \quad t \in [0,t_f]$ with the set of admissible controls (admissible set) denoted as V_{ad}. The proof of the existence of the optimal solution was done using the following theorem.

2.1.3 Theorem. *There exists an optimal solution* $(x^*,V^*) \in W^{1,\infty}([0,t_f],\mathbb{R}^4) \times L^\infty([0,t_f],\mathbb{R})$ *for the optimal problem such that* $J(V) = \max_{V \in V_{ad}} J(v)$, *where* $x^* = [E^*,T^*,N^*,\mu^*]^T$ *if the following conditions are satisfied*

1. *The set of admissible state is nonempty.*
2. *The admissible set* V_{ad} *is nonempty, convex and closed.*
3. *There exits constants* $h_2,h_3 > 0$ *and* $b > 1$ *such that* $L(E,T,v) \leq h_2 - h_3(|v|)^b$ Rihan et al. (2014).

An efficient numerical technique employing forward and backward approximation schemes to the adjoint system was used to solve the optimality problem and identify the best combination treatment strategy. Numerical results showed and affirmed that indeed optimality treatment strategies can decrease the loading of tumour cells and result in an increment of effector cells just after a few days of treatment. However, the study was limited by the fact that it did not take into consideration the delays in both the state and control variables when the optimal control system was subjected to mixed control state constraints.

Pang et al. (2016) in their paper discussed single chemotherapy and immunotherapy and mixed treatment as well as conditions triggering tumour eradication. They analysed the effects of least effective concentration and the half-life of the therapeutic drugs where they found that better results can be achieved if the half-life of the drug is extended. Further, the impact of drug resistance on therapeutic results was considered and a mathematical model explaining the cause of chemotherapeutic failure that uses a single drug was proposed. In the end, numerical simulations showed that chemoimmunotherapy is likely to achieve a better treatment effect. However, despite the reported achievement, tumour cells are increasingly becoming resistant to numerous structurally and mechanistically unrelated drugs, limiting the efficacy of chemotherapy. Thus the open problem of how to effectively amalgamate those treatment modes and design optimal mixed therapeutic regimen deserves further research.

2.2 Models of Chemovirotherapy

Malinzi (2019) proposed a mathematical model for chemovirotherapy where he considered three-drug infusion methods and compared their efficacies, performed mathematical analysis to forecast the outcomes of the OVs in combination with chemotherapy and also compared the efficacy of each single

treatment modality. The model was investigated for each treatment with each infusion function and stability was investigated for time-invariant solutions so as to identify the conditions for which its possible to achieve tumour free state. The model was formulated based on two aspects, that is, model without delay and delay model. In the construction of mathematical model without delay, a number of factors were considered in a confined avascular tumour including infected tumour cells $I(t)$, uninfected tumour cells denoted by $U(t)$, chemotherapeutic $C(t)$ drug and free virus density population $V(t)$. It was assumed that the uninfected tumours develop logistically with an intrinsic rate of α measured daily and K being the carrying capacity of cells. The rate at which the infected cells die out is represented by δ and the virus replication is typified by $\beta U(t)V(t)$, where β denotes virus multiplication rate per day. The terms $\delta_0 U(t)C(t)$ and $\delta_1 I(t)C(t)$ represents in the respective order the response emanating from the uninfected tumour and infected tumour as a result of drug infusion with δ_0 and δ_1 indicating lysis rates per day. $\frac{1}{\gamma}$ represents the lifespan of the virus with its production taken as $b\delta I$ where b denotes the virus burst size measured per day and δ is the rate of death of infected tumour cells per day. The function $g(t)$ models the chemotherapeutic drug's infusion with the rate of depletion from body tissues being λ. The model takes the form

$$\begin{aligned} U'(t) &= \alpha U(t)\left(1-\frac{U(t)+I(t)}{K}\right)-\beta U(t)V(t)-\delta_0 U(t)C(t),\\ I'(t) &= \beta U(t)V(t)-\delta I(t)-\delta_1 I(t)C(t),\\ V'(t) &= b\delta I(t)-\beta U(t)V(t)-\gamma V(t),\\ C'(t) &= g(t)-\lambda C(t). \end{aligned} \tag{2.2.1}$$

Simulation of drug infusion in the body was done using three methods: a sinusoidal function $g(t) = q\sin^2(at)$, a constant rate $g(t) = q$ and an exponential $g(t) = q\exp(-at)$ where q represents drug infusion rate and the constant a indicates how the exponential drug decays and the period for the sinusoidal function.

The delay model due to the delays of the infection of tumours by virus and chemotherapy drug responses is given below

$$\begin{aligned} U'(t) &= \alpha U(t)\left(1-\frac{U(t)+I(t)}{K}\right)-\beta U(t-\tau_1)V(t-\tau_1)-\delta_0 U(t-\tau_2)C(t-\tau_2),\\ I'(t) &= \beta U(t-\tau_1)V(t-\tau_1)-\delta I(t)-\delta_1 I(t-\tau_2)C(t-\tau_2),\\ V'(t) &= b\delta I(t)-\beta U(t-\tau_1)V(t-\tau_1)-\gamma V(t),\\ C'(t) &= g(t)-\lambda C(t). \end{aligned}$$

In order to determine the efficacy of each treatment and their amalgamations, the dynamics of the system under no treatment at all was given, in which it was shown that the tumour develops to its maximum size. The model was then tested with virotherapy, chemotherapy and both treatments, where it was deduced that with a constant drug infusion and no virotherapy, no complete elimination of the tumour occurs and a fraction of the drug still remains in the body.

When $V(t) = 0$, that is no virotherapy then we have the following system of equations

$$\begin{aligned} U'(t) &= \alpha U(t)(1-U(t))-\delta_0 U(t)C(t),\\ C'(t) &= \xi(t)-\psi C(t). \end{aligned} \tag{2.2.2}$$

The following results by Malinzi (2019), were arrived at

2.2.1 Theorem. *The system of equations in (2.2.2), with constant infusion, has no periodic solutions for positive* $U(t)$ *and* $C(t)$.

The boundedness and positive invariance were based on the following theorem.

2.2.2 Theorem. *If* $U(0) \geq, I(0) \geq 0, V(0) \geq 0$, *and* $C(0) \geq 0$, *then* $U(t) \geq 0, I(t) \geq 0$ *and* $C(t) \geq 0$ *for all* $t \geq 0$.

Other important results are given below.

2.2.3 Theorem. *The trajectories evolve in an attracting region* $\mathbb{D} = \{(U, I, V, C) \in \mathbb{R}^4_+ | U(t) + I(t) \leq 1, V(t) \leq (\frac{b}{\gamma}), C(t) \leq C(\phi)\}$, *where* $C(\phi)$ *depends on the drug infusion function used.*

2.2.4 Theorem. *The domain* $\mathbb{D}$ *is positive invariant for the model for the system (2.2.1) and therefore biologically meaningful for the tumour, virus and drug cell concentrations.*

Numerical simulations for both models were performed using ode23s and dd23 in MATLAB, where it was shown that if the tumour burst is big, then regardless of the drug infusion method, chemovirotherapy is efficacious than any of the single treatments. Further, simulations showed that incorporating delays in the system increased the time within which the tumour clearance occurred in the body tissue. Despite this study, there still exist open questions which need further studies: the model does not address the quantity of dose required to completely eradicate the tumour and at what specific point in the tumour should the drug be infused to have a greater effect. Interestingly, ascertaining of the optimal dosing and dosing schedule still, pose a challenge.

In an attempt to describe the spatiotemporal dynamics of tumour cells, Malinzi (2015) proposed a spatiotemporal mathematical model to simulate avascular tumour growth under chemovirotherapy treatment. The model aimed at finding the outcome of combining drugs and OVs so as to eradicate tumours from the body tissue as well as to determine the most influential and critical parameters during the admission of chemovirotherapy treatment. The model considered the Kolmogorov equation to simulate the movement of cells. Travelling wave solutions revealed that the rate of tumour growth, the rate at which infected tumour cell die, cell diffusion constants and the rate at which virus and drug decays are the critical parameters under chemovirotherapy. Further, numerical solutions showed that chemovirotherapy can eliminate tumours rapidly compared to monotherapies.

Malinzi et al. (2015) formulated a mathematical model that described the interactions of the tumour-immune-virus dynamics. In their model they incorporated local kinetic interaction terms of the tumour and immune cells and a modified functional immune response to account for the saturation of immune cells in a tumour. The results from their study indicated that the main virotherapy treatment properties were tumour cell movement and local kinetic interaction terms such as tumour growth and death rates.

The study was later extended in Malinzi et al. (2017) to include parabolic non-linear PDEs to examine the spatiotemporal dynamics of tumour cells under the treatment of chemovirotherapy. The model considered avascular solid tumour under the presumption that spherical coordinates are radially symmetrical. The model was analyzed for both temporal and spatiotemporal cases where travelling wave solutions to the spatiotemporal model were utilized to find the minimum wave speed of tumour influx. A sensitivity analysis was done on the parameters of the model to determine parameters that play a significant role in tumour remission during chemovirotherapy treatment. After the analysis of the temporal model was performed it was established that the success of the virotherapy is determined by the rate of virus infection and virus burst size and solutions of the spatiotemporal model in the form of travelling wave revealed that tumour diffusivity and growth rate are critical parameters during chemovirotherapy. However, the model assumed some of the key aspects of biology majorly the immune response that is

known to impact the development of the tumour upon their invasion. The study is limited to a 1-D spatial domain, limiting the description of the tumour. The study did not also take into account the interactions of the tumour with its microenvironment and therefore did not look into cytotoxicity effects of chemotherapy on normal cells. The model did not investigate what happens prior to the tumour's maximum growth and thus further study is needed to incorporate these aspects.

In an effort to investigate the enhancement of chemotherapy by virotherapy, Malinzi et al. (2018) proposed an ODE mathematical model and an optimal control problem using chemovirotherapy. The model described the interplays between tumour cells, immune response and a treatment combination by combining virotherapy and chemotherapy. Stability analysis showed that tumours could grow to their maximum capacity given that there is no form of treatment. It was shown that chemotherapy alone is likely to clear tumour cells on the condition that the efficacy of the drug is more than the intrinsic growth rate of the tumour. The combined effects of oncolytic virus and chemotherapy were evaluated using forward sensitivity index to perform a sensitivity analysis in regard to critical parameters of chemotherapy. An optimal control problem was proposed and investigated with the quadratic objective function applied to determine the optimal dosage amalgamation of the virotherapy and the chemotherapy drug to control the tumour. The control variables $u_1(t)$ and $u_2(t)$ were set to respectively represent the supply of viruses from an external source of the drug dosage. The control system is stated as follows

$$\begin{aligned}
\frac{dU}{dt} &= \alpha U\left(1-\frac{U+I}{k}\right)-\frac{\beta UV}{K_u+U}-\frac{\delta_U UC}{K_c+C},\\
\frac{dI}{dt} &= \frac{\beta UV}{K_u+U}-\delta I-\frac{\delta_1 IC}{K_c+C},\\
\frac{dV}{dt} &= b\delta I-\frac{\beta UV}{K_u+U}-\gamma V+u_1(t),\\
\frac{dC}{dt} &= u_2(t)-\psi C(t),
\end{aligned} \tag{2.2.3}$$

where U, I, V, C represents respectively the uninfected tumour density, infected tumour cell, free virus particles and drug concentration. α is the tumour growth rate, b is the virus burst size, K_u and K_c are Michael Menten constants, ψ is the rate of drug decay, δ_U is the lysis rate of U by the drug, δ_I represents the lysis rate of I by the drug, γ is the rate of virus decay and K is the tumour carrying capacity.

The optimal control combination $(u_1(t), u_2(t)$ was determined to adequately minimize the total tumour density as well as the cost of treatment. The objective functional was to maximise

$$J(u_1,u_2)=\int_0^{T_f}\left[U(t)+I(t)+\left(\frac{A_1u_1^2(t)}{2}+\frac{A_2u_2^2(t)}{2}\right)\right]dt,$$

where T_f represents the termination time of the treatment and A_1 and A_2 are basically the relative measures of both the cost needed to implement each of the related controls as well as the negative impacts of the treatment. Thus the optimal control pair is sought in such a away that

$$J(u_1^*,u_2^*)=\min\{J(u_1,u_2)|(u_1,u_2)\in M\},$$

where M is the control set given by $M=\{(u_1.u_2)|u_i$is measurable with $0\le u_i(t)\le u_i^{MTD}, \quad t\in[0,T_f], \quad i=1,2\}$ where u_1^{MTD} represents the maximum number of viruses that the body tissue can contain and u_2^{MTD} represents the maximum tolerated dose. These may generally be viewed on a broader

basis to be the maximum amounts a patient can afford financially. Sufficient conditions for the existence of a solution to the quadratic optimal control problem was examined using the following result.

2.2.5 Proposition. There exists an optimal control pair (u_1^*, u_2^*) with a corresponding solution (U^*, I^*, V^*, C^*) to the model system $2.2.3$ minimizing $J(u_1, u_2)$ over M.

The optimal control problem was solved using the Pontryagin's Maximum Principle with numerical solutions to the optimal control problem conducted to determine the optimal dosages required to minimize chemo-virus combination. This analysis showed that optimal drug and the combination drug coincide with half their maximum tolerated doses. Simulations indicate that the success of chemovirotherapy depends on virus burst size, the rate of viral infection and the dose which is in line with recent studies. Moreover, the right dose of chemotherapy required to produce effective results in unison with virotherapy has been a concern for both clinicians and mathematicians. Additionally, the question of the optimal therapeutic drug and the virus dosage combinations needed to eradicate the tumour has not been answered. Numerical simulations indicated that with chemovirotherapy tumour eradication is likely to occur in less than a month, a result which is unrealistic. Other questions that are still open include figuring out the most successful method of drug infusion and the fundamental treatment characteristics. The study can be extended to include more biological facets such as spatial variations of the cell concentration. In addition, it would be imperative to extend the study to investigate the effect of toxicity of viruses and the drug on normal body tissue.

Rihan et al. (2014) developed a delay differential model with optimal control elucidating the interplays of immune and tumour cells coupled with external therapy. The model incorporated optimal control variables with the goal of determining the best treatment strategy with minimal side effects. They established the existence of an optimal control pair and the optimality system where they utilized Pontryagin's maximum principle to classify optimal controls. The model took into account the penetration of tumour cells by effector cells and numerical results indicate that a load of tumour cells is reduced by the optimal treatment strategies while effector cells are increased few days following the therapy. However, how to combine immunotherapy and chemotherapy effectively still remains an open question yet to be explored. More work needs to be done to include sophisticated problems incorporating delays in both state and control variables.

2.3 Models of Chemoradiotherapy

In a study by Goldie and Coldman Goldie et al. (1988), a stochastic model for alternating radiation and chemotherapy was proposed. Their model was based on the earliest approaches for combination therapy where they used three compartments, that is, stem, differentiation and end cells in modelling tumour growth. Their model incorporated chemo-resistant, radio-resistant and extra parameters to measure cells with joint resistance. Surprisingly, their concept of varying chemo-resistant, radio-resistant and their joint resistance has never been incorporated into other chemoradiotherapy models. They found that a regimen treatment with three doses of chemotherapy and radiotherapy acting in an alternating manner is powerful compared to sequential treatment under the same conditions because it suppresses subpopulation resistant responsible for treatment failure. The fact that the model did not consider the host's response would disqualify the model from quantifying complete survival and thus the model only predicts qualitative interrelationships between the regimen.

In another study by Beil and Wein (2002), a mathematical model was formulated with the aim of determining the best way to sequence the three standard therapies for cancer: radiotherapy, chemotherapy

and surgery as an optimal control problem. Differential equations were used to model the growth of tumours and its metastases with an underlying assumption that the primary and metastatic tumour have identical behaviour. The model keeps track of the temporal development of the tumour and its associated metastases and the local cell kill was used to model effects caused by the treatment. The model aimed to show which combination achieved higher curative probability: SCR (surgery first then chemotherapy then radiotherapy), SRC (Surgery then radiotherapy then chemotherapy) and SRCR (Surgery then radiotherapy then chemotherapy then radiotherapy) given that the primary tumour is big enough or that the metastatic cancer population outnumbers the primary tumour. Their model included metastatic cancer originating from dormant cells and angiogenesis, which eventually led to the interactions between primary tumour compartment and metastatic compartment and thus the emergence of optimality sequences, Medina-Echeverz and Berraondo (2012). It was shown that SRCR is better than SCR and SRC and that if the metastatic is high then it is advisable to use SCR otherwise its recommendable to use SRC. They also proposed new SRCR which incorporated splitting radiotherapy treatment regimen to maximize the probability of tumour control for certain conditions of vascular growth. Despite the model's 14 parameters making it hard to infer from the clinical data, the large sets of data make it possible to give qualitative recommendations in nature.

Ergun et al. (2003) used a similar approach to find optimal scheduling and doses of angiogenic inhibitors and radiotherapy that maximize the elimination of primary tumour. The model was validated into two compartments of tumour cells and vascular endothelial cells and the damage by radiation was modelled in accordance with the linear-quadratic (LQ) which widely determines fractionation schedules in radiobiology society. The study makes it possible to give more quantitative predictions on the sequence of biological agent and radiation and dosing schedule. It was shown that optimal amalgamation treatment regimen happens when antiangiogenetic therapy is constantly increased in order to maintain an optimal tumour endothelial cells ratio, and the fraction sizes of radiation keep changing with treatment so as to maximize the probability of tumour control. However, the model was solely concerned with the primary tumour and did not include the antimetastatic effect of antiangiogenic treatment, which might inhibit metastatic growth during radiotherapy if it's applied methodically. Further, the model did not take into consideration the fact that radiation may cause vascular endothelial growth factor (VEGF) expression, which attenuates the destruction of endothelial cells by radiotherapy.

Salari et al. (2015) extended BED (biologically effective dose) model to include a single linear term in chemotherapy dose and a multiplicative term which is linear in radiotherapy dose. He showed that the addition of chemotherapy drug and its mode of action makes optimal fractionation regimen change for concurrent chemoradiotherapy. They conclude that introduction of chemotherapeutic drugs containing cytotoxic effects only do not hamper optimal fractionation regimen when there is no concurrent chemotherapy whereas a radiosensitization agent has the capacity to tamper with the optimality choice of fraction size. They also show that the emergence of optimal non-uniform fractionation may result if a drug exhibits both radiosensitization and independent cytotoxic properties, Medina-Echeverz and Berraondo (2012). Their study explicitly included drug and radiotherapy effects in the healthy tissue, where they not only drew conclusions of high tumour cell destruction but also high therapeutic index from various fractionation schedules.

Ghaffari et al. (2016) proposed an ODE model that considered chemotherapy and radiotherapy and metastatic cancer. They examined the interaction between the immune and cancer cells, with chemotherapy regarded as a predator on both normal and cancer cells. It was assumed that the interplay between tumor cells and NK cells changes during the chemotherapy. The model aimed at understanding the specific system dynamics as well as to guide the development of combination therapies. Both numerical and analytical analysis of the model was done. It was shown that the decaying dosage protocol is weaker

compared to the constant dosage protocol in eliminating small metastases at a given time. Thus, the study indicated that the development of combination chemoradiotherapy protocols for treating certain forms of cancer represents a suitable strategy in cancer treatment research.

2.4 Models of Radioimmunotherapy

O'Donoghue et al. (2000) proposed a Uniform Tumor Dosimetry mathematical model that compared single-dose and fractionated radioimmunotherapy. The model compared large single administrations (LSAs) with rapid fractionation (RF) administered in small quantities within a short period of the time interval. Alternative treatments with identical absorbed doses to red marrow were compared through the integrated compartment model responsible for treating pharmacokinetics and tumour response.

In a study by Kumar and Kumar (2010), a new mathematical model which included linear and exponential partially depending on tumour parameters was developed for radioimmunotherapy. The designing of the model included a term for the immune response in the presence of radiotherapy. They formulated radiotherapy dose distributions with regard to optimizing tumour cure probability (TCP) where the rate of dose distribution was presumed to be high enough to enable the delivery of dose distribution instantaneously. Numerical results showed that the density of a tumour cell and dose distribution are not sensitive to other various functional forms of tumour parameters. The study explained in detail the effects of immune response with radiotherapy in the tumour treatment with results revealing that immune response plays a critical role in the treatment of a tumour.

Flux et al. (1997) described a dosimetry 3-D mathematical model that quantified the absorption of dose distribution as a result of administration of an intralesional radiolabeled monoclonal antibody which allowed the distribution of spatial and temporal heterogeneity of radionuclide without a calibration scan. The model developed basically shows how an activity is distributed as a function of time as a result of infusion at a single point within the tumour. The model used parameters which are either known or obtained from SPECT image data. The model was tested by using a set of registered patient data where dose profiles and histograms of the dose volume were produced. It was established that 3-D dose distribution was significantly non-uniform. Initially, intralesional infusion results suggested that the model offered a means of determining how the absorbed dose was distributed within a tumour.

Serre et al. (2016) suggested a discrete-time pharmacodynamic mathematical model of the amalgamation of radiotherapy and immune checkpoint inhibitors: PD1–PDL1 axis and the CTLA4. The model comprises of a simplified model of tumour growth mixed with antitumor immune response. The system describes numerous experimental outcomes concerning the interrelationship between the immunogenicity of a tumour and its mass dynamics. This framework gives an account on why tumour immunogenicity initially rises with the mass, but disappears as soon as the inflammatory tumour microenvironment (TME) gets progressively more immunosuppressive The model shows how a growing tumour triggers and inhibits tumour immune response and described the effects of irradiation using the linear-quadratic model. The model explains why discontinuation of immunotherapy may either lead to durable sustained response or tumour recurrence. The model's ability to predict pharmacodynamic endpoints was retrospectively validated based on whether it reproduces in silico using data obtained from experimental studies. They concluded that different designs in silico could be compared by simulating Kaplan–Meier curves and mathematical tools could be used to partially automate optimized protocols. More work is needed to focus on integrating the developed mathematical methods into clinical practice that will heavily deal with managing drug and radiation-induced toxicities during the process of optimization.

Further, an investigation on Dose-effect relationships and a pharmacokinetic model should be combined to give an account of the relationship between the experimental results and the actual dosing protocols.

2.5 Models of Immunovirotherapy

Shen et al. (2002) developed a mathematical model of tumour clonogenic cell kinetics based on the lysis of the cells by radiation, the proliferation of cells and accelerated doubling time for tumour during treatment. The model was used to predict the toxicity of the bone marrow and tumour management for any given time after dosage for any fractionation scheme and tumour radiopharmacokinetics. Optimal dosing scheme was determined as well as tumour management for marrow toxicity. His model was basically for mouse marrow and tumour because of the ease with which it can be validated in future experiments. Results showed that for any amount of injected radioactivity, fractionated administration caused less bone marrow toxicity compared to single-dose injection.

Timalsina et al. (2017) proposed a mathematical model based on PDEs with the aim of studying tumour virotherapy and mediated immunity. The model incorporated adaptive and innate immunity responses with interactions in tumour cells, OVs and immune system in a territory containing a boundary in motion. Extensive numerical simulations of the model were done with the help of well designed computational methods. They assumed that all tumour cells exhibit homogeneity and viruses follow a diffusion process. They used the results obtained to examine tumour development and provide insight into crucial aspects of virotherapy such as dependence of the efficacy on vital parameters and the delay in the adaptive immunity.

Jenner et al. (2018) suggested a mathematical model with a view to reproducing the results for tumour growth synonymous to results produced experimentally during treatment with an oncolytic adenovirus co-expressing the immunostimulatory cytokines interleukin 12 (IL-12) and granulocyte-monocyte colony stimulating factor (GM-CSF). They explored the heterogeneity in the simulation treatment of immune cell where they found a subset of parameter space where the treatment will be less effective for a short time interval. The concept of heterogeneity was used to explain the bivariate nature of treatment outcome where the tumour either grew unbounded or was completely eliminated. The presence of negative feedback in the T cell and APC stimulation dynamics was highlighted. The model was fitted into data using the parameters from the literature in order to reduce the degrees of freedom of the model. Optimization of the model was done using a least-squares non-linear fitting algorithm 'lsqnonlin' in MATLAB. The model indicates that decreasing APC stimulation and raising helper T cell stimulation is likely to improve the treatment. However an open question still exists: for what range of these parameters does the absolute elimination of tumor cells occur?

Wares et al. (2015) built a mathematical model of tumour dynamics to investigate the efficacy of combining oncolytic adenoviruses injections with dendritic cell injections with the aim of examining different treatment strategies. The model consisted of a system of ODEs and was fitted to the hierarchical data, where parameter estimation based on the availability of experimental information in literature was done before fitting the data. The model was used to check effects of varying the doses of the oncolytic virus. It was assumed that the diameter of tumour cells was approximately 0.01 mm and that apart from the initial uninfected tumour cells populations which are fitted to the experimental data, all other populations are initially zero. The results indicated that using a slightly larger dose could absolutely eradicate the tumour. Furthermore, it was suggested that using immunostimulatory oncolytic viruses first then followed by a sequence of dendritic cells (DC) is more effective compared to alternating OV and DC injections. This approach enables the infection to thrive before the enhancement of an immune

response. It was concluded that the efficacy of a dosing strategy depends on the ordering of oncolytic adenoviruses and dendritic cells, temporal tumour spacing and the dosage of oncolytic adenoviruses and dendritic cells.

The model was later extended by Gevertz and Wares (2018), where they explored if the earlier model was the minimal model required to precisely describe the data. They used different techniques such as information criteria analyses, sensitivity analyses and a parameter sloppiness analysis where they discovered that it is possible to reduce their model to one variable and three parameters and still be fitted to the data. They argued that reduction of the model to minimal form allows for easy tractability of the system in the face of parametric uncertainty.

Mahasa et al. (2017) presented a mathematical model that elucidated the interplays between OV, tumour cells, normal cells and the antitumoral and antiviral immune responses. The model consisted of DDEs with one discrete delay indicating the time required to trigger a tumour-specific immune response. The model aimed to predict effects of antitumoral and antiviral immune responses in the presence of OV, the response of the tumour to the oncolytic viral infections and the OV tumour-specificity responsible for maximizing the reduction of the tumour while concurrently ensuring that the toxicity on the normal tissue encircling tumour cells are minimized. It was shown that global sensitivity analysis gave indispensable insights regarding parameter's influence on growth kinetics and how the tumour responds to OVs. Their findings bolster the designing of OVs with higher oncolytic potency to tumour cells compared to normal cells and have a high capacity to recruitment adaptive antiviral and antitumoral immune responses. The model did not look at spatial intratumoral heterogeneity and thus a study to extend the model to incorporate spatial intratumoral heterogeneity is pertinent as it is stipulated that tumour heterogeneity hamper the diffusion of a virus within tumour cells.

? formulated a tumour growth and viral oncology mathematical model that incorporated immune recruitment to promote the eradication of tumours. The model explicitly included heterogeneity in tumour cell cycle time span by utilizing a distributed DDEs. The interrelationship between the estimated number of cells surviving in the cell cycle and tumour eradication was established by the help of linear stability analysis. It was shown that immune tumour interactions results in the expansion of the tumour and that immune inclusion are pertinent in deducing long-term response to virotherapy. However, the model was limited by the fact that it oversimplified tumour immune interplays and immune response so as to analytically manage the model and the study did not take into account the interplays between the immune cells in the tumour and cytokine's legions. One of the open questions that exist is in determining the best distribution for modelling the tumour cell cycle durations.

2.6 Models of Radiovirotherapy

Dingli et al. (2006) proposed a mathematical model considering population dynamics that encapsulated crucial components of radiovirotherapy. The model described the said interactions and the model functions were fitted with experimental data recently published for immunocompromised mice. They first introduced the model of untreated tumour growth by using Bertalanffy-Richards model, then the model of a tumour with virotherapy and the model was extended to incorporate effects of radiovirotherapy. Stability analysis of the equilibrium points in relation to partial cure, absolute cure and therapy cure was presented and prove and typical bifurcations was done. Their study aimed to construct a model for radiovirotherapy and then use the model to predict the outcome of cancer treatment. They presented simulations which described dynamical elements of radiovirotherapy and virotherapy as well as elements of optimization. They also evaluated relevant therapeutic scenarios for radiovirotherapy and presented

parameters for optimization. In modelling tumour growth in the presence of virotherapy their model at time $t = t_v$ is given by

$$\begin{aligned} y' &= ry\left(1 - \frac{(x+y)^\epsilon}{K^\epsilon}\right) - kyv, \quad y(t_v) = y_v, \\ x' &= kyv - \delta x \quad x(t_v) = 0, \\ v' &= \alpha x - \omega v, \quad v(t_v) = v_0, \end{aligned}$$

with $y(t)$ representing population dynamics of uninfected tumor cells, $x(t)=$ virus infected tumor cells and $v(t) =$ free infectious virus particles. The term kyv represents the rate at which the infected cells leave the population of uninfected cells and enter the population of infected cells. The model was modified to include the radiation after time $t = t_r$ with the presumption that radiation affects both infected and uninfected cells in equal measure. The population of irreparably destroyed cells by radiation $u(t)$ was introduced and $D(t)$ denotes the radiation dose. The model is presented as shown below:

$$\begin{aligned} y' &= ry\left(1 - \frac{(x+y+u)^\epsilon}{K^\epsilon}\right) - kyv - \beta D_y, \quad y(t_r) = y_r, \\ x' &= kyv - \delta x, -\beta D_x, \quad x(t_r) = x_r, \\ u' &= \beta D(x+y) - \gamma u^v, \quad u(t_r) = 0, \\ v' &= \alpha x - \omega v, \quad v(t_v) = v_r, \end{aligned}$$

where $D = \eta\lambda \int_{t_r}^{t} I_T(t')dt'$ with I_T representing the amount of radioactive iodide that are present at the tumor site, γu^v denotes the effective rate of death of annihilated cells. β represents the rate constant for tumor cells becoming irreparably damaged. The model was validated by the means of least square method so as to fit the available data extracted from multiple myeloma induced by mice.

Parameter estimation was done by employing a weighted non-linear least square method using MLAB and MAPLE. Simulations indicated that the lower the equilibrium tumour burden the oscillations are less likely to be dumped and their frequency of occurrence is high. Some combinations of parameters were found to exhibit dynamical fluctuations. Simulations suggested that parameters describing viral infectivity, cytotoxicity and proliferation were confined in a limited range. It was concluded that the maximum benefit of radiation is subject to the amount of iodine taken up and retained by the tumour and the initial viral dose partly determines the maximum tumour burden and the response time.

Tao and Guo (2007) developed a PDE model describing cancer radiovirotherapy, which is a generalization of the existing ODE model given in Dingli et al. (2006). The model comprised of modelling tumour volume as an incompressible fluid. A prove of global existence and uniqueness to the solutions of the model was given and a parameter condition corresponding to this therapy was explicitly given. Numerical simulations revealed that radiovirotherapy is an effective mode of cancer treatment compared to virotherapy alone. Numerical simulations also showed that there exists optimal timing for radio-iodine administration. There is a need for more studies to incorporate space heterogeneity to the model described in this study.

Lai and Friedman (2017), in their study considered a combination therapy where one drug was used as a vaccine to activate dendritic cells so as to instigate more T cells for the purpose of invading the tumour while the other drug is a checkpoint inhibitor which suppresses cancer cells. They developed a mathematical model in the form of PDEs to address the question of whether combining treatment of two drugs administered at certain levels is better than using a treatment of one drug with almost

twice the dosage level. The model is based on how dendritic cells, cancer cells, cytokines IL-I2 and IL-2, $CD8^+$ cells (T_8), GM-CFC-secreting cancer cells (GVAX) and anti-PD-1 interact. It is tacitly assumed that $CD4^+$T cells, cancer cells (C), $CD8^+$ cells (T_8) and dendritic cells are constant in spatiotemporal and the equation for each was suggested. The concept of synergy between drugs was introduced and a synergy map was developed suggesting the proportion in which drugs should be administered so as to realize the maximum tumour volume to be reduced under the restriction of a maximum tolerated dose. The model was simulated by the help of Matlab by using moving mesh method for solving PDEs with free boundary. Results showed that combining GVAX and anti-PD-1 in suitable quantities could consequentially reduce the growth of a tumour. More studies needs to be carried out to explore the effects of treatment with GM-CFC-secreting vaccine (GVAX) and anti-PD-1 drug.

Other mathematical models of combination cancer therapy include that of Bozic et al. (2013), where a mathematical model was formulated to predict the outcomes of amalgamation of targeted therapies on tumors using the data derived from 20 melanoma patients. Kozłowska et al. (2018) presented a comprehensive stochastic mathematical model and simulator approach to describe platinum resistance and standard-of-care (SOC) therapy in high-grade serous ovarian cancer (HGSOC). Sun et al. (2016) developed a a multiscale mathematical model framework consisting of a set of stochastic differential equations to describe pharmacokinetics, cellular dynamics, and progression-free survival at the patient level while accounting for microenvironment adaptations. Araujo et al. (2005) utilized mathematical modelling to explore amalgamation therapy where multiple nodes in a signal transduction pathway were targeted concomitantly with specific inhibitors. Hadjiandreou and Mitsis (2014) developed a mathematical model that used Gompertz growth law and pharmacokinetic-pharmacodynamic approach to model the effects of drugs on tumor progression tumor bearing mice and they also designed optimal therapeutic patterns. Su et al. (2016) formulated a new mathematical model of tumor therapy with oncolytic virus and MEK inhibitor. Kim and Lee (2012) modelled interactions at the tumour site by utilizing an agent-based model (ABM) and dynamics in the lymph node using a system of delay differential equations (DDEs). Bajzer et al. (2008) modelled cancer virotherapy with recombinant measles viruses where the interactions of the tumour and virus were based on the already established biology.

3. Plausible combinations and open questions

3.1 Plausible Combinations

For many years treatment modalities involving monotherapy have been used as a treatment regimen to cure cancer. However, these treatment modalities often leave a patient with severe side effects with cancer cells developing resistance against them and devising mechanisms to evade immunosurvellance recognition. Combination therapy is likely to be the key to counter these effects and resistance to drugs. Much concern has been raised over the toxicity and effectiveness of any combination therapy. Ideally, there are several factors that necessitate the selection of a certain cancer combination therapy such as improvement in the quality of life of the patient, nonoverlapping safety profiles, reduction of drug resistance and preclinical evidence of synergy between the interacting therapeutic agents, Miles et al. (2002). However, rarely are these criteria met, Miles et al. (2002). Ultimately, since in most cases the combination components are administered at suboptimal doses due to dose-limiting toxicities, combination therapy have often failed to record significant improved outcomes. It's generally agreed that some forms of cancer are incurable and treatment is only administered to improve the quality of life and prolong life. In this respect, a combination that proves clinically to be of benefit to the patient taking into account the cost incurred will highly prove valuable. Thus in this project, a rationally designed combination will be selected based on a number of factors such as the efficacy, the overall survival benefits to the patients, reduction of toxicity, the impact on the tumour, the complexity of the combination and the overall cost of the combination model. To this end, we discuss the plausible cancer treatment combinations in the journey to bring sanity in cancer treatments.

3.1.1 Radiovirotherapy. This form of combination treatment regiment has shown significantly improved results when used to treat cancer and it has been employed in many occasions to treat prostate cancer, lung cancer, malignant mesothelioma, cervical cancer, glioblastoma and cholangiocarcinoma, Ottolino-Perry et al. (2010). Several combinations have been made in vitro to with the hope of improving the quality of life, for example, the amalgamation of external radiotherapy with prostate specific adenovirus CV706 had a huge impact on the prostate specific antigen within the first 6 weeks resulting to a significant regression in tumour in mice 8 weeks post-treatment, Ottolino-Perry et al. (2010). A combination of radiotherapy and NV1066 virus signifcantly reduced the tumour mass for malignant mesothelioma and nonsmall cell lung cancer, Ottolino-Perry et al. (2010). Treatment of cervical cancer with G207 and exernal radiotherapy completely saw its complete elimination 30 days post treatment in mice, Ottolino-Perry et al. (2010). However, there was no significant better results in both immunocompetent and immunocompromised models for prostate cancer when radiotherapy was in unison with herpes virotherapy. The potential for radiovirotherapy is yet to be seen in other types of cancer, Ottolino-Perry et al. (2010).

Despite these encouraging results, the efficacy of radiovirotherapy can be limited by several factors in thyroid tumour treatment. The biodistribution of the virus, its propagation in the tumour through numerous replication cycles and the strength of the sodium/iodide symporter (NIS) expression can be inadequate or heterogeneous and thus it may affect an effective therapeutic response, Touchefeu et al. (2012). Furthermore, there is a risk that the therapeutic schedule may be suboptimal with the administration of radioisotope happening before or after the climax of NIS expression, Touchefeu et al. (2012). Additionally, the rate of dosage and the total amount of the dose given could be restricted by the efflux radioiodide from the cells where low dose levels may render the tumour radioresistant, Touchefeu et al. (2012). One of the problems of the application of radiotherapy is its inhibitory effect on the viral

replication and hence does not enhance the efficacy. Administering of radiotherapy 7 days postinfection decreased antitumour effect to a greater extent compared to adminstration 1 or 4 days postinfection ascertaining that a proper timing could impact the efficacy of the therapy, Ottolino-Perry et al. (2010). Radiovirotherapy recorded overall survival improvement in the above aforementioned cancers despite severe side effects such as gastrointestinal toxicity and weight loss.

3.1.2 Chemoradiotherapy (CRT). The use of chemoradiotherapy has increased substantially over the last few years to treat various forms of cancer including the locally-advanced head and neck squamous cell carcinoma (HNSCC) and Non-small-cell lung cancer (NSCLC). Nevertheless, the overall long-term survival for this therapy has been rather disappointing with insignificant results on the overall survival ,Ottolino-Perry et al. (2010). Chemoradiotherapy results to severe side effects with the disease recurring again within a short period of time upon its administration. Although CRT enhances local tumor control, there is little evidence to ascertain the survival benefit of conjoining chemotherapy to radiation in aged patients with locally or regionally advanced HNSCC, Baxi et al. (2016). Chemoradiotherapy has also been tested in the treatment of cervical cancer where concurrent chemoradiotherapy has been shown to reduce the risk of cancer recurring by 50% in patients having advanced stage disease regional spread, or high-risk features after hysterectomy but neoadjuvant chemotherapy followed by radiotherapy have failed to indicate overall survival significance in spite of the high doses of chemotherapy, Eifel (2006).

Although chemoradiotherapy has been promising in the treatment of cervical cancer, its introduction induced new challenges, Eifel (2006). Incidences of recurrence, gastrointestinal and severe hematologic complications have greatly increased thus the need to closely monitor patients throughout treatment, an activity which is not only costly but tiresome, Eifel (2006). Due to limitations in the availability of data, it has always been hard to ascertain the complications emanating from chemoradiotherapy, Eifel (2006). Although CRT was thought of as an alternative for surgery in the treatment of localized esophageal cancer, its application has limited effect because of the low survival in the surgery alone arm, Neuner et al. (2009). RIT has low overall survival rate and late toxicity, thus it is believed that a multimodality approach including chemotherapy before surgery or chemoradiotherapy is likely to improve the survival of patients with esophageal cancer, Shitara and Muro (2009).

3.1.3 Radioimmunotherapy (RIT). Radioimmunotherapy treatment regimen has been used in the treatment of haematological malignancies with a fractionated dosing regimen achieving a remarkable regressions of bulky masses with non-Hodgkin lymphoma, Sharkey and Goldenberg (2011). Despite a reported success in the subsequent trials with various antibodies in lymphoma, RIT was inhibited by haematological toxicity since radiolabled antibody disappeared steadily from the blood, subjecting the radiosensitive bone marrow to a perpetual low-dose irradiation, Sharkey and Goldenberg (2011). Another disappointing results of RIT is that it is likely to cause secondary cancers and myelodyplastic syndrome (MDS), Sharkey and Goldenberg (2011), thereby endangering the lives of patients in addition to introducing new complications to their life. Several studies on other aggressive non-Hodgkin lymphoma have indicated promising efficacy of anti-CD20 radioimmunotherapy and anti-CD22 radioimmunotherapy, Kraeber-Bodéré et al. (2016). Nonetheless, despite the reported success, the adoption of radioimmunotheray has never happened in the medical community mainly because of concerns about secondary myelodysplasia/acute leukemia risk, inadequate randomized studies, existence of numerous novel competing targeted agents such as ibrutinib or idelalisib and failure of oncohematologists to use the therapy in their own departments, Kraeber-Bodéré et al. (2016). Clinical efficacy of RIT applications in solid tumours remain limited and there is only inadequate randomized study that has been published, Kraeber-Bodéré et al. (2016).

Some of the benefits associated with RIT include reduced haematologic toxicity, improved survival and improved efficacy with RIT, however, still some resistance develops. All these aspects show that RIT

is highly promising and is likely to contribute significantly to the overall survival for patients with solid tumors, Kraeber-Bodéré et al. (2016). One of the pitfall of RIT is that it could be costly and can lead to severe side effects to few patients, hence the need to preselect patients with high affinity of responding, Kraeber-Bodéré et al. (2016). Convincing of the oncohematologist community to incorporate RIT would require designing of randomized clinical trials and stratification of patients for response to radioimmunotherapy, Kraeber-Bodéré et al. (2016).

3.1.4 Chemovirotherapy. Chemovirotherapy treatment regimen constitutes diverse mechanisms of action and therefore it is regarded as a more likely approach in overcoming resistance mechanisms. This combination permits possible lowering of the applied therapeutic agents which subsequently reduces toxicity, and cuts cost significantly. Several experimental studies have been conducted on chemovirotherapy and it has been established that the right combinations of chemotherapeutic agents and oncolytic viruses results in synergistic interactions and thus enhancing therapeutic effects not achievable when each therapy is used alone, Ottolino-Perry et al. (2010). Chemovirotherapy has found its way in the treatment of malignant gliomas, lymphoma, lung and metastatic breast cancer. In one experimental study, combining oncolytic adenovirus (ICOVIR-5) with either everolimus (RAD001) or temozolomide (TMZ) showed an enhanced increment of the anti-glioma effect in vitro and in vivo glioma xenograft model, Ottolino-Perry et al. (2010).

In a mice model of colon cancer, combination of cyclophosphamide (CPA) with measles virus resulted in 100% survival cases after 90 days of treatment and complete regression in 9 out of 10 animals in comparison to only 30% with either therapy alone, Ottolino-Perry et al. (2010) Development of adenovirus-based chemovirotherapeutic regimens have notably indicated an enhanced anti-tumor effect of H101 in unison with cisplatin and 5-fluorouracil (5-FU) compared to chemotherapy alone in phase II/III in the treatment of head and neck cancer patients, Binz and Lauer (2015).

A combination of adenovirus and CPA tested in a mice showed a significant improvement of overall survival, enhanced efficacy and decreased tumour volume however a similar combination involving low dose CPA and oncolytic reovirus showed numerous immune modulating effects. An ex vivo combination of other chemotherapeutic agents and viruses in the treatment of various cancers indicated a result of significant survival, improved tumor regression and a reduction of metastases as evidenced in, Ottolino-Perry et al. (2010). Although this combination has proved promising, its however limited by the side effects such as viremia and cardiac toxicity. However to counter delays in response of both the chemotherapeutic and virus which increases the time needed to clear the tumour, a combination of viruses and drugs should be designed to minimize the delays, Malinzi (2019). Although there are few clinical trials on chemovirotherapy currently, the aforementioned combinations are promising and calls upon clinical review.

3.1.5 Chemoimmunotherapy. Presently there does not exist treatments for Chronic Lymphocytic Leukemia (LLC), however chemoimmunotherapy has been shown to achieve disease control and survival prolongation, Brown et al. (2016). However, despite this reported potential in CCL treatment, chemoimmunotherapy has several disadvantages. One of the concerning effects that results from this combination is that of secondary malignancies. It also leads to myelo- and immunosuppression which are likely to be the onset of myeloid malignancies (acute myeloid leukemia [AML] and myelodysplastic syndrome [MDS]), Brown et al. (2016). In the treatment of metastatic melanoma, chemoimmunotherapy was employed and devastating results were obtained with overall survival not improved in comparison with that of chemotherapy alone, Sasse et al. (2007). Furthermore, people treated with chemoimmunotherapy recorded increased hematological and non-hematological toxicities.

In contrast to the combinations described above, chemovirotherapy represents a rationally designed

combination due to the improved overall survival benefits, nonoverlapping safety profiles, reduction of drug resistance, the impact on the tumour and of note is the preclinical evidence of synergy between the components. Other factors that led to the above decision is the cost involved where chemovirotherapy requires relatively low cost and the time required for tumour regression as well as the time needed to neutralise the resulting side effects is relatively low in comparison with other combination regimens. In support of this are the several mathematical models on chemovirotherapy that have been presented. The excellent paper of Malinzi (2019) on mathematical analysis of chemovirotherapy, indicated that the tumour is likely to be cleared from the body in less than a month if both chemotherapy and virotherapy are used, implying that the quality of life will be improved and life will be prolonged. Further, the study contended that in the treatment of cancer oncolytic viruses enhances chemotherapeutic drugs which is also in agreement with Malinzi et al. (2018).

3.2 Open problems

We anticipate our understanding of the mechanisms of operations of cancer to ameliorate in the near future, but the success will depend on multidisciplinary of sections across ecology, epidemiology, genetics and immunology. The earlier euphoria following breakthroughs exploiting combination therapy has been tainted by the existence of numerous challenges. To this end, we highlight the outstanding open problems that still exist despite the reported success and numerous efforts in the research community to combat cancer using combination anti-cancer therapy.

Notwithstanding the notable success reported both clinically and experimentally, much is still not known about chemovirotherapy, Malinzi et al. (2018). The principal mechanisms underlying the anti-tumoral effects of many ordinary virotherapies in conjunction with chemotherapeutics still remains a mystery. Fundamental questions such as prospective ramifications of chemotherapeutic agents on viral replication and the immunotherapeutic effects caused by virotherapy are yet to be answered. Another troubling problem is that of fully distinguishing chemotherapy-related toxicity from that of virotherapy induced toxicity, Binz and Lauer (2015). Designing optimal scheduling of chemovirotherapy treatment attracts questions in an attempt to decipher the right dose combination, deciding the most effectual method of drug infusion and the critical treatment characteristics, Malinzi et al. (2018). Furthermore, figuring out the potential implications of chemotherapeutics on viral reproduction and/or the immunotherapeutic effects possibly caused by virotherapeutics is never easy, Binz and Lauer (2015). Combinations related to chemotherapy produce compounded toxicity and bone-marrow suppression and therefore their potential remains to be seen.

In spite of the growing expectations, combination ant-cancer therapy exhibits inconsistency activity, which can be attributed to the problems incurred when conjoining these molecularly targeted agents, Tolcher and Mayer (2018). It's however hard to establish whether the heterogeneity of response can be ascribed to the complications of tumour biology, poor drug penetration into the tumour or suboptimal/uncoordinated exposure to the conjoined agents, Tolcher and Mayer (2018). Furthermore, the problem of determining the ratio at which therapeutic agents should be mixed to produce maximal synergistic and minimal anti-cancer effects is unanswered. The problems of how to find drug best combinations, as well as how to effectively combine therapy ex vivo in human cells to avoid doing thousands of clinical trials is still disturbing.

It will be interesting to know how to effectively combine therapeutic agents to produce effective results with appropriate sequencing of these agents. It is likely that amalgamating two or more therapies will probably compound the effects to the patients if not optimally designed and thus the challenge

of optimally reducing these agents to circumvent the resulting side effects to a tolerable level is of great concern. This is likely to lead to suboptimal administration of drugs and thus encouraging drug resistance in the course of the treatment. However, in clinical trials, it has always been essential to de-escalate the dose until the drugs become ineffective, a process which is time-consuming and laborious.

Although radioimmunotherapy is a promising treatment protocol, questions regarding its long-term safety issues still exist. Despite the RIT being one of the treatment modalities with ease in tumour detection, there still exist difficulties in speculating responses based on dosimetry and radiobiological models, Sharkey and Goldenberg (2011). An understanding of how these treatments can be best administered, how frequent the treatments can be administered and how to best integrate them with other agents to increase the overall response is yet to be developed, Sharkey and Goldenberg (2011). In spite of the fact that it is still possible to administer higher doses of radioactivity, it is still not known if the ratio of the tumour to that of non-tumour is higher. In addition, practical questions such as ascertaining the efficacy of the amalgamation specifically the abscopal effect, how to sequence the combination to give the best result and determining the optimal timing of the amalgamation are still open.

Chemoimmunotherapy remains a suitable treatment modality option for patients with Chronic Lymphocytic Leukemia. However many practical questions including how to optimally sequence the therapeutic agents, how to assess the optimal length of therapy and comprehending responses with class switching, as well as questions focusing on the mechanisms of overcoming resistance still remain open for further study Brown et al. (2016).

4. Conclusion and future work

While there has been some remarkable achievement and promise in the utilization of mathematical models in the combination treatment of cancer, there is still a long way left to go. Since cancer is a complex disease, its biology and development are poorly understood and thus mathematical models thus far developed are relatively simple focusing on some aspects of the interplays of the tumour and immune response with external therapies. The complexities associated with cancer after treatment are a worry and no combination treatment has been tested clinically to effectively cure cancer mainly because of the cost involved and the complexities involved. Thus a novel combination treatment selected for cancer treatment should significantly reduce the mass of the tumour, increase the overall survival of a patient, reduce drug resistance, increase the efficacy and show preclinical evidence of synergy.

Mathematical modelling is making a significant contribution to the treatment of cancer. Using a combination treatment regimen in advanced cancer setting is increasingly more debatable. Thus given the pressure to find a value-based healthcare cancer treatment therapy, there is absolutely no qualm that mathematical approach will be an integral tool in determining the best combination regimen at a reduced cost while improving the outcome in the years to come. However, despite the promising results reported in various studies towards cancer treatment, most of them have not been integrated for clinical use.

It is a widely acknowledged fact that defeating cancer is unlikely to happen from a single therapeutic agent but rather a reasonable amalgamation of harmonious compatible strategies chosen from diverse therapeutics including immunotherapeutics, radiotherapy, chemotherapeutics, targeted therapies and antiangiogenic agents. Ideally, there is a dire need to optimize dosing, duration as well as relative scheduling of the diverse components by considering the potential synergies and the probable antagonisms and toxicities. With the numerous possibilities of combinatorial therapies and the outstanding challenge of figuring out the interplays between complex and intricated pharmacologic processes, we trust that optimization of these amalgamations in silico before testing them in patients could be made possible by developing an integrated mathematical model. This model will play an essential role in deciding on strategies that are viable both medically and economically with a high likelihood of yielding clinical benefit.

We believe that there is every reason to remain confident and optimistic. With the advent in technologies such as gene-silencing tools and phosphoproteomic technologies, the understanding and prediction of intricate compensatory signalling mechanisms would be made easier as it is likely to influence scientists into proposing and predicting effective combinations in a faster note without much ado. Furthermore, designing clinical trials reflecting on the toxicities and the usage of intermittent dosing and designing of an adaptive trial to allow the ever-changing combinations concerning the emergence of resistance will definitely lead into a more effective combination cancer therapy that improves the quality of life of the patients.

Since many cancer deaths are related to drug resistance and metastases, developing a cure for cancer is arguably one of the most difficult tasks both in the clinical and scientific community. Thus drugs that aim to prolong life should be given an upper hand in the clinical set-up and hence it is a matter of time to see if investment in developing drugs that render tumours dormant will be made.

Acknowledgements

I would like to take this opportunity to thank the Almighty Lord for seeing me through this project. I am highly thankful for Dr Malinzi for his active guidance through the completion of this project. I would also like to thank AIMS fraternity for giving me a chance to advance my studies and the numerous guidance that came along during my stay at AIMS, South Africa. I'm also indebted to my fellow students who extended a helping hand when the going got tough and above all, who always uttered a word of encouragement when giving up was inevitable. My other special thanks goes to my family and relatives who believed in me and who tirelessly offered insurmountable support before and during my AIMS stay. Thank you all for making an impact in my life. Your memory shall forever linger and be part of my life.

References

Araujo, R., Petricoin, E., and Liotta, L. A mathematical model of combination therapy using the egfr signaling network. *Biosystems*, 80(1):57–69, 2005.

Bajzer, Ž., Carr, T., Josić, K., Russell, S. J., and Dingli, D. Modeling of cancer virotherapy with recombinant measles viruses. *Journal of Theoretical Biology*, 252(1):109–122, 2008.

Baskar, R., Lee, K. A., Yeo, R., and Yeoh, K.-W. Cancer and radiation therapy: current advances and future directions. *International Journal of Medical Sciences*, 9(3):193, 2012.

Baxi, S. S., O'Neill, C., Sherman, E. J., Atoria, C. L., Lee, N. Y., Pfister, D. G., and Elkin, E. B. Trends in chemoradiation use in elderly patients with head and neck cancer: Changing treatment patterns with cetuximab. *Head & Neck*, 38(S1):E165–E171, 2016.

Beil, D. R. and Wein, L. M. Sequencing surgery, radiotherapy and chemotherapy: Insights from a mathematical analysis. *Breast Cancer Research and Treatment*, 74(3):279–286, 2002.

Binz, E. and Lauer, U. M. Chemovirotherapy: Combining chemotherapeutic treatment with oncolytic virotherapy. *Oncolytic Virotherapy*, 4:39, 2015.

Bozic, I., Reiter, J. G., Allen, B., Antal, T., Chatterjee, K., Shah, P., Moon, Y. S., Yaqubie, A., Kelly, N., Le, D. T., et al. Evolutionary dynamics of cancer in response to targeted combination therapy. *eLife*, 2:e00747, 2013.

Brown, J. R., Hallek, M. J., and Pagel, J. M. Chemoimmunotherapy versus targeted treatment in chronic lymphocytic leukemia: when, how long, how much, and in which combination? *American Society of Clinical Oncology Educational Book*, 36:e387–e398, 2016.

Cassidy, T. and Humphries, A. R. A mathematical model of viral oncology as an immuno-oncology instigator. *Mathematical Medicine and Biology: A Journal of the IMA*, 04 2019. ISSN 1477-8599. doi: 10.1093/imammb/dqz008. URL https://doi.org/10.1093/imammb/dqz008.

Chan, W.-l., Lam, K.-o., Siu, W.-k., and Yuen, K.-k. Chemotherapy at end-of-life: An integration of oncology and palliative team. *Supportive Care in Cancer*, 24(3):1421–1427, 2016.

Chappell, M., Chelliah, V., Cherkaoui, M., Derks, G., Dumortier, T., Evans, N., Ferrarini, M., Fornari, C., Ghazal, P., Guerriero, M., et al. Mathematical modelling for combinations of immuno-oncology and anti-cancer therapies. In *Quantitative Systems Pharmacology UK Meeting, Macclesfeld*, 2015.

Collins, C., Fister, K., and Williams, M. Optimal control of a cancer cell model with delay. *Mathematical Modelling of Natural Phenomena*, 5(3):63–75, 2010.

de Pillis, L., Renee Fister, K., Gu, W., Collins, C., Daub, M., Gross, D., Moore, J., and Preskill, B. Mathematical model creation for cancer chemo-immunotherapy. *Computational and Mathematical Methods in Medicine*, 10(3):165–184, 2009.

de Pillis, L. G. and Radunskaya, A. A mathematical model of immune response to tumor invasion. In *Computational Fluid and Solid Mechanics 2003*, pages 1661–1668. Elsevier, 2003.

Deng, L., Liang, H., Burnette, B., Beckett, M., Darga, T., Weichselbaum, R. R., and Fu, Y.-X. Irradiation and anti–pd-l1 treatment synergistically promote antitumor immunity in mice. *The Journal of Clinical Investigation*, 124(2):687–695, 2014.

Dingli, D., Cascino, M. D., Josić, K., Russell, S. J., and Bajzer, Ž. Mathematical modeling of cancer radiovirotherapy. *Mathematical Biosciences*, 2006.

Dry, J. R., Yang, M., and Saez-Rodriguez, J. Looking beyond the cancer cell for effective drug combinations. *Genome Medicine*, 8(1):125, 2016.

Eifel, P. J. Chemoradiotherapy in the treatment of cervical cancer. In *Seminars in radiation oncology*, volume 16, pages 177–185. Elsevier, 2006.

Ergun, A., Camphausen, K., and Wein, L. M. Optimal scheduling of radiotherapy and angiogenic inhibitors. *Bulletin of Mathematical Biology*, 65(3):407–424, 2003.

Flux, G. D., Webb, S., Ott, R. J., Chittenden, S. J., and Thomas, R. Three-dimensional dosimetry for intralesional radionuclide therapy using mathematical modeling and multimodality imaging. *Journal of Nuclear Medicine*, 38(7):1059–1066, 1997.

Galluzzi, L., Vacchelli, E., Bravo-San Pedro, J.-M., Buqué, A., Senovilla, L., Baracco, E. E., Bloy, N., Castoldi, F., Abastado, J.-P., Agostinis, P., et al. Classification of current anticancer immunotherapies. *Oncotarget*, 5(24):12472, 2014.

Gevertz, J. L. and Wares, J. R. Developing a minimally structured mathematical model of cancer treatment with oncolytic viruses and dendritic cell injections. *Computational and Mathematical Methods in Medicine*, 2018, 2018.

Ghaffari, A., Bahmaie, B., and Nazari, M. A mixed radiotherapy and chemotherapy model for treatment of cancer with metastasis. *Mathematical methods in the Applied Sciences*, 39(15):4603–4617, 2016.

Goldie, J., Coldman, A., Ng, V., Hopkins, H., and Looney, W. A mathematical and computer-based model of alternating chemotherapy and radiation therapy in experimental neoplasms1. In *Treatment modalities in lung cancer*, volume 41, pages 11–20. Karger Publishers, 1988.

Grassberger, C. and Paganetti, H. Methodologies in the modeling of combined chemo-radiation treatments. *Physics in Medicine & Biology*, 61(21):R344, 2016.

Hadjiandreou, M. M. and Mitsis, G. D. Mathematical modeling of tumor growth, drug-resistance, toxicity, and optimal therapy design. *IEEE Transactions on Biomedical Engineering*, 61(2):415–425, 2014.

Hu, Q., Sun, W., Wang, C., and Gu, Z. Recent advances of cocktail chemotherapy by combination drug delivery systems. *Advanced Drug Delivery Reviews*, 98:19–34, 2016.

Isaeva, O. and Osipov, V. Different strategies for cancer treatment: mathematical modelling. *Computational and Mathematical Methods in Medicine*, 10(4):253–272, 2009.

Jenner, A. L., Yun, C.-O., Yoon, A., Coster, A. C., and Kim, P. S. Modelling combined virotherapy and immunotherapy: strengthening the antitumour immune response mediated by il-12 and gm-csf expression. *Letters in Biomathematics*, 5(sup1):S99–S116, 2018.

Jeon, M., Kim, S., Park, S., Lee, H., and Kang, J. In silico drug combination discovery for personalized cancer therapy. *BMC Systems Biology*, 12(2):16, 2018.

Karev, G. P., Novozhilov, A. S., and Koonin, E. V. Mathematical modeling of tumor therapy with oncolytic viruses: effects of parametric heterogeneity on cell dynamics. *Biology Direct*, 1(1):30, 2006.

Kim, P. S. and Lee, P. P. Modeling protective anti-tumor immunity via preventative cancer vaccines using a hybrid agent-based and delay differential equation approach. *PLoS Computational Biology*, 8 (10):e1002742, 2012.

Kirschner, D. and Panetta, J. C. Modeling immunotherapy of the tumor–immune interaction. *Journal of Mathematical Biology*, 37(3):235–252, 1998.

Kozłowska, E., Färkkilä, A., Vallius, T., Carpén, O., Kemppainen, J., Grénman, S., Lehtonen, R., Hynninen, J., Hietanen, S., and Hautaniemi, S. Mathematical modeling predicts response to chemotherapy and drug combinations in ovarian cancer. *Cancer Research*, 78(14):4036–4044, 2018.

Kraeber-Bodéré, F., Barbet, J., and Chatal, J.-F. Radioimmunotherapy: from current clinical success to future industrial breakthrough? *Journal of Nuclear Medicine*, 57(3):329–331, 2016.

Kumar, D. and Kumar, S. A mathematical model of radioimmunotherapy for tumor treatment. *African journal of Mathematics and Computer Science Research*, 3(6):101–106, 2010.

Lai, X. and Friedman, A. Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: A mathematical model. *PloS One*, 12(5):e0178479, 2017.

Lai, X., Stiff, A., Duggan, M., Wesolowski, R., Carson, W. E., and Friedman, A. Modeling combination therapy for breast cancer with bet and immune checkpoint inhibitors. *Proceedings of the National Academy of Sciences*, 115(21):5534–5539, 2018.

Lopez, J. S. and Banerji, U. Combine and conquer: challenges for targeted therapy combinations in early phase trials. *Nature Reviews Clinical Oncology*, 14(1):57, 2017.

Mahasa, K. J. *Mathematical Modelling of Tumour-Immune Interactions and Cancer Therapy*. Phd, University of Stellenbosch, 2017.

Mahasa, K. J., Eladdadi, A., De Pillis, L., and Ouifki, R. Oncolytic potency and reduced virus tumor-specificity in oncolytic virotherapy. a mathematical modelling approach. *PloS One*, 12(9):e0184347, 2017.

Malinzi, J. *Mathematical modeling of cancer treatments and the role of the immune system response to tumor invasion.* PhD thesis, 2015.

Malinzi, J. Mathematical analysis of a mathematical model of chemovirotherapy: Effect of drug infusion method. *Computational and Mathematical Methods in Medicine*, 2019, 2019.

Malinzi, J., Sibanda, P., and Mambili-Mamboundou, H. Analysis of virotherapy in solid tumor invasion. *Mathematical Biosciences*, 263:102–110, 2015.

Malinzi, J., Eladdadi, A., and Sibanda, P. Modelling the spatiotemporal dynamics of chemovirotherapy cancer treatment. *Journal of Biological Dynamics*, 11(1):244–274, 2017.

Malinzi, J., Ouifki, R., Eladdadi, A., Torres, D. F., and White, K. Enhancement of chemotherapy using oncolytic virotherapy: Mathematical and optimal control analysis. *American Institute of Mathematical Sciences*, 15(6):1435–1463, 2018.

Medina-Echeverz, J. and Berraondo, P. How can chemoimmunotherapy best be used for the treatment of colon cancer? *Immunotherapy*, 4(12):1787–1790, 2012.

Miles, D., von Minckwitz, G., and Seidman, A. D. Combination versus sequential single-agent therapy in metastatic breast cancer. *The Oncologist*, 7(Supplement 6):13–19, 2002.

Mokhtari, R. B., Homayouni, T. S., Baluch, N., Morgatskaya, E., Kumar, S., Das, B., and Yeger, H. Combination therapy in combating cancer. *Oncotarget*, 8(23):38022, 2017.

National Cancer Institute. Precision medicine in cancer treatment. National Cancer Institute, https://www.cancer.gov/about-cancer/treatment/types/precision-medicine., Accessed May 2019.

Neuner, G., Patel, A., and Suntharalingam, M. Chemoradiotherapy for esophageal cancer. *Gastrointestinal Cancer Research: GCR*, 3(2):57, 2009.

O'Donoghue, J. A., Sgouros, G., Divgi, C. R., and Humm, J. L. Single-dose versus fractionated radioimmunotherapy: model comparisons for uniform tumor dosimetry. *Journal of Nuclear Medicine*, 41(3):538–547, 2000.

Ottolino-Perry, K., Diallo, J.-S., Lichty, B. D., Bell, J. C., and McCart, J. A. Intelligent design: combination therapy with oncolytic viruses. *Molecular Therapy*, 18(2):251–263, 2010.

Page, K. Mathematical modelling of tumour dormancy. *Mathematical Modelling of Natural Phenomena*, 4(3):68–96, 2009.

Pang, L., Shen, L., and Zhao, Z. Mathematical modelling and analysis of the tumor treatment regimens with pulsed immunotherapy and chemotherapy. *Computational and Mathematical Methods in Medicine*, 2016, 2016.

Pillis, D., G., L., and Radunskaya, editors. *A Mathematical Tumor Model with Immune Resistance and Drug Therapy: An Optimal Control Approach*. Journal of Theoretical Medicine, 2001.

Rihan, F. A., Abdelrahman, D., Al-Maskari, F., Ibrahim, F., and Abdeen, M. A. Delay differential model for tumour-immune response with chemoimmunotherapy and optimal control. *Computational and Mathematical Methods in Medicine*, 2014, 2014.

Rodrigues, D. S., Mancera, P. F. d. A., Carvalho, T., and Gonçalves, L. F. A mathematical model for chemoimmunotherapy of chronic lymphocytic leukemia. *Applied Mathematics and Computation*, 349: 118–133, 2019.

Salari, E., Unkelbach, J., and Bortfeld, T. A mathematical programming approach to the fractionation problem in chemoradiotherapy. *IIE Transactions on Healthcare Systems Engineering*, 5(2):55–73, 2015.

Sasse, A. D., Sasse, E. C., Clark, L. G., Ulloa, L., and Clark, O. A. C. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. *Cochrane Database of Systematic Reviews*, (1), 2007.

Serre, R., Benzekry, S., Padovani, L., Meille, C., André, N., Ciccolini, J., Barlesi, F., Muracciole, X., and Barbolosi, D. Mathematical modeling of cancer immunotherapy and its synergy with radiotherapy. *Cancer Research*, 76(17):4931–4940, 2016.

Sgouros, G. Plasmapheresis in radioimmunotherapy of micrometastases: a mathematical modeling and dosimetrical analysis. *Journal of Nuclear Medicine: official publication, Society of Nuclear Medicine*, 33(12):2167–2179, 1992.

Sharkey, R. M. and Goldenberg, D. M. Cancer radioimmunotherapy. *Immunotherapy*, 3(3):349–370, 2011.

Shen, S., Duan, J., Meredith, R. F., Buchsbaum, D. J., Brezovich, I. A., Pareek, P. N., and Bonner, J. A. Model prediction of treatment planning for dose-fractionated radioimmunotherapy. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, 94(S4):1264–1269, 2002.

Shitara, K. and Muro, K. Chemoradiotherapy for treatment of esophageal cancer in japan: current status and perspectives. *Gastrointestinal Cancer Research: GCR*, 3(2):66, 2009.

Spring, B. Q., Lang, R. T., Kercher, E. M., Rizvi, I., Wenham, R. M., Conejo-Garcia, J. R., Hasan, T., Gatenby, R. A., and Enderling, H. Illuminating the numbers: Integrating mathematical models to optimize photomedicine dosimetry and combination therapies. *Frontiers in Physics*, 7:46, 2019.

Steel, G. G. and Peckham, M. J. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. *International Journal of Radiation Oncology* Biology* Physics*, 5(1):85–91, 1979.

Su, Y., Jia, C., and Chen, Y. Optimal control model of tumor treatment with oncolytic virus and mek inhibitor. *BioMed Research International*, 2016, 2016.

Sun, X., Bao, J., and Shao, Y. Mathematical modeling of therapy-induced cancer drug resistance: connecting cancer mechanisms to population survival rates. *Scientific Reports*, 6:22498, 2016.

Tao, Y. and Guo, Q. A free boundary problem modelling cancer radiovirotherapy. *Mathematical Models and Methods in Applied Sciences*, 17(08):1241–1259, 2007.

Timalsina, A., Tian, J. P., and Wang, J. Mathematical and computational modeling for tumor virotherapy with mediated immunity. *Bulletin of Mathematical Biology*, 79(8):1736–1758, 2017.

Tolcher, A. W. and Mayer, L. D. Improving combination cancer therapy: the combiplex® development platform. *Future Oncology*, 14(13):1317–1332, 2018.

Touchefeu, Y., Franken, P., and J Harrington, K. Radiovirotherapy: principles and prospects in oncology. *Current Pharmaceutical Design*, 18(22):3313–3320, 2012.

Wares, J. R., Crivelli, J. J., Yun, C.-O., Choi, I.-K., Gevertz, J. L., and Kim, P. S. Treatment strategies for combining immunostimulatory oncolytic virus therapeutics with dendritic cell injections. *Mathematical Biosciences & Engineering*, 12(6):1237–1256, 2015.

Yan, L., Rosen, N., and Arteaga, C. Targeted cancer therapies. *Chinese Journal of Cancer*, 30(1):1, 2011.