Advancing Tumor Control: The Promise of Adaptive Therapy

by

Harley I. Richker

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Carlo Maley, Chair
Carolyn Compton
Melissa Wilson

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ABSTRACT

This review aims to provide a comprehensive review of the most recent literature on adaptive therapy, a promising new approach to cancer treatment that leverages evolutionary theory to prolong tumor control[1]. By capitalizing on the competition between drug-sensitive and drug-resistant cells, adaptive therapy has led to a paradigm shift in oncology. Through mathematical and *in silico* models, researchers have examined key factors such as dose timing, cost of resistance, and spatial dynamics in tumor response to adaptive therapy. With a partial focus on preclinical experiments involving ovarian and breast cancer, this review will discuss the demonstrated effectiveness of adaptive therapy in improving progression free survival and tumor control. Through the review process, it was determined that dose modulation outperformed drug-vacation strategies, emphasizing the significance of tumor heterogeneity and spatial structure in accurately modeling adaptive therapy mechanisms. The potential of ongoing clinical trials to improve patient outcomes and long-term treatment efficacy is emphasized, while a thorough analysis of study methodologies shapes the future direction of adaptive therapy research.

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CHAPTER 1

INTRODUCTION

Adaptive therapy is a novel approach to cancer treatment that leverages evolutionary theory to inhibit the development of drug resistant cells. In this treatment, instead of providing the typical maximum effective drug dose, the reduced doses are given. The goal of this is to maintain the tumor at a stable and manageable level. This treatment allows competition between treatment sensitive cells and treatment resistant cells, leading to tumor stability over a longer period of time[2]. This personalized approach enables doctors to adjust treatment plans according to tumor response. Cancers evolve and adapt to different environments – creating the ability to evade both the immune system and therapies. By monitoring the tumor response to treatment, adaptive therapy is able to utilize the dynamic between the immune system, drug sensitive cells, and drug resistant cells, in order to maintain control over the drug resistant cells[3].

The use of pesticides by farmers provides unique insight to this problem of therapeutic resistance. Initially, farmers would give high doses of pesticides to eradicate all pests. However, it was found that this ultimately led to stronger, uncontrolled pest strains. The process then shifted to allot minimum possible doses to prevent the development of resistance. This new practice lends insight into the Darwinian dynamics that minimize pest populations[4].

Since its introduction by Dr. Robert Gatenby in 2009, adaptive therapy has gained significant interest as a promising therapeutic regimen. Initially, mathematical models verified that treatment resistant cells arise from small, less fit populations within the tumor

before treatment. Therefore, maximum tolerated dose (MTD) treatments select for resistance by killing all sensitive cells that were initially more fit. Adaptive therapy confronts this complication by not killing all sensitive cells to compete with the less fit chemoresistant cells, holding them at bay. This treatment-for-stability strategy prolongs survival compared to MTD and metronomic therapies in models. *In vivo* application of this model was supported by maintenance of small tumor size in an ovarian cancer mouse model[5].

As a novel cancer treatment regimen, continued research was essential to further understanding the mechanisms behind the initial results. Previous reviews[2-4] on the topic were limited by the knowledge available at the time. Numerous preclinical and mathematical modeling studies have been developed since which have led to the refinement of *in silico* models[6], multi-drug applications[7], and human clinical trials[8] (*Fig.1*). In this examination, we will analyze the current state of adaptive therapy and its open questions[3].

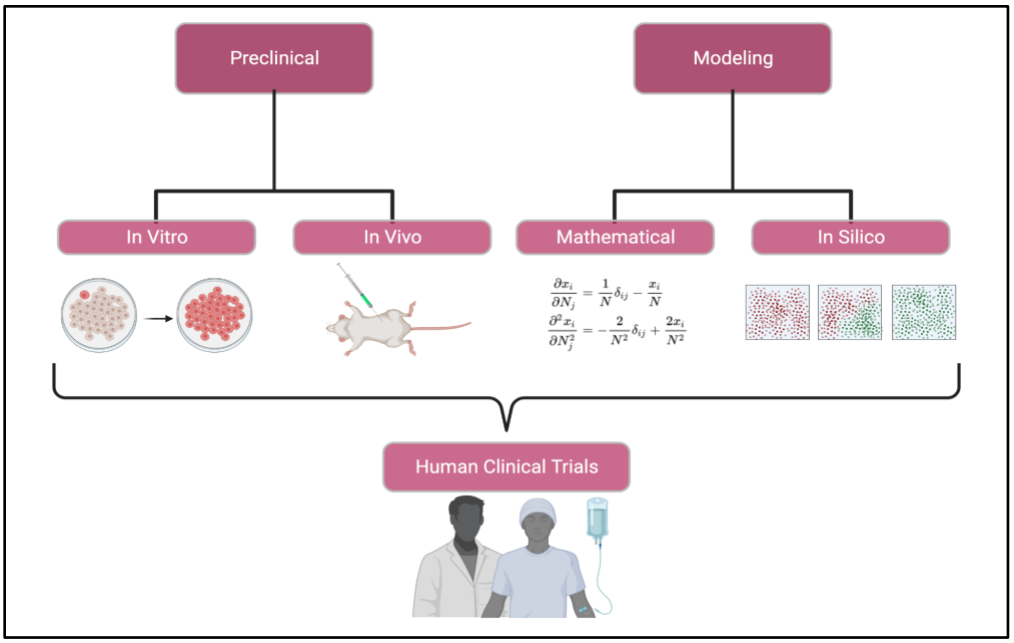

Figure 1. Breakdown Of Study Methodologies. Summary of adaptive therapy study methodologies; all of which inform the design of human clinical trials.

For decades, cancer has been treated by administering treatment at a maximum tolerated dose. Oncologists have traditionally applied cancer therapies in this way with the goal of eradicating all the cancer cells in the body. Applying maximum tolerated doses has worked on some occasions, but it is common that the cancer cells evolve resistance, and the medication stops working for the patient (*Fig.2A*).

Metronomic cancer therapies are designed to apply the minimum effective dose (MED) of therapy for prolonged periods without causing high toxicity[9]. Metronomic therapies are effective to prevent tumor growth and metastases. Overall, the therapy has been successful in improving patient quality of life, but it is not exempt from the evolution of resistance (*Fig.2B*). Although cancer cells can still become resistant with metronomic cancer therapies, adaptive cancer therapy can slow down the progression of resistance[9] and maintain stable competition between sensitive and resistant cells (*Fig.2C*).

Adaptive therapy shifts the clinical goal from tumor eradication to prolonged tumor control, focused on limiting the emergence of therapeutic resistance. Adaptive therapy applies an effective dose rather than a max dose, to slow down cancer cell evolution and keep a balance of sensitive and resistant cells. Ultimately this keeps cancer responsive to cancer but never resistant[5].

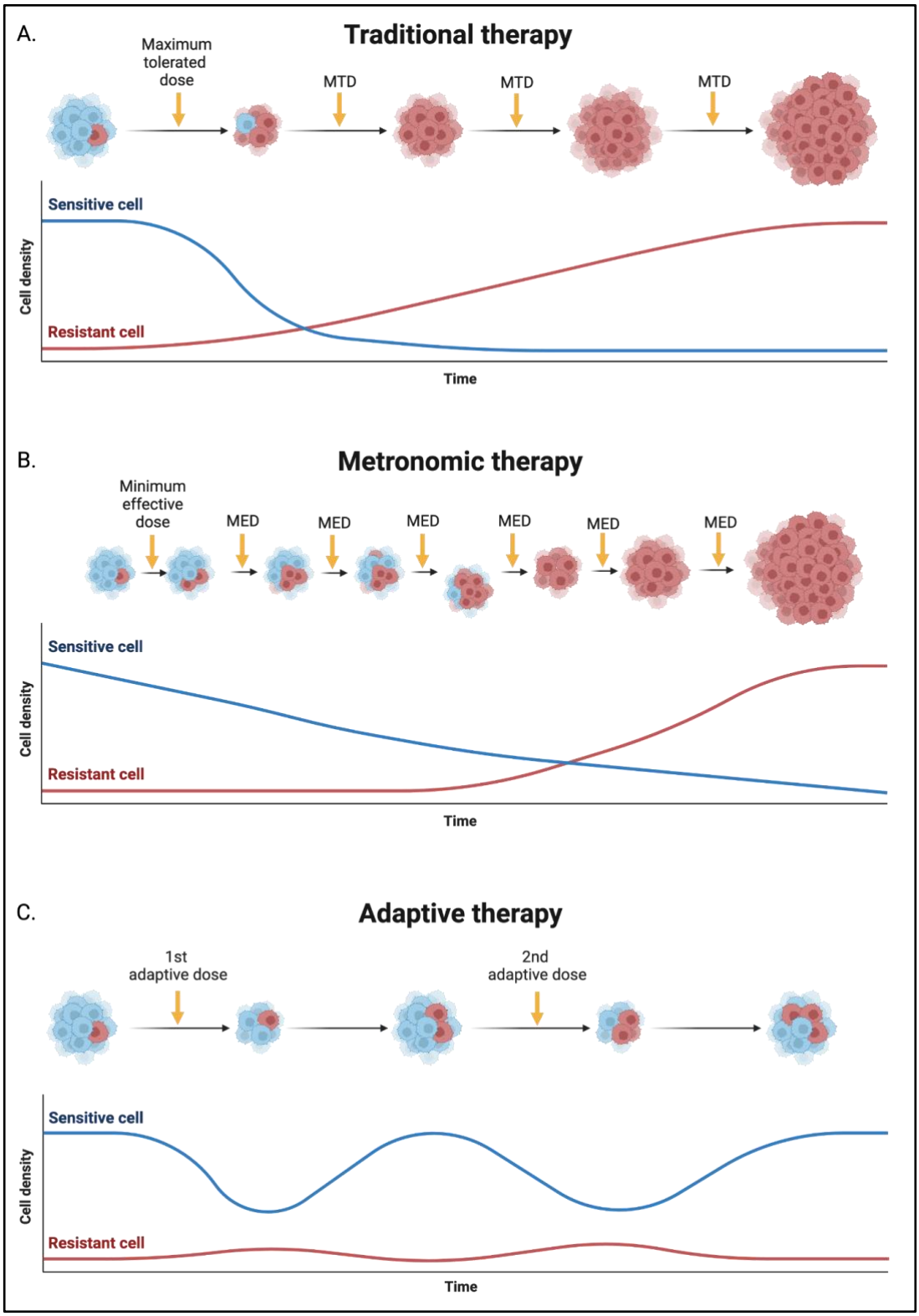

Figure 2. Comparison Of Cancer Treatment Regimens. Cell densities of sensitive and resistant populations for (a) standard therapy with maximum tolerated dosing (MTD) (b) intermittent therapy with minimum effective dosing (MED) and (c) adaptive therapy with drug vacation dosing.

CHAPTER 2

MODELING STUDIES

Mathematical Models

Mathematical modeling of cancer provides an excellent framework to test and explore the efficacy of adaptive therapy protocols. These models have informed the development of clinical experiments and applications. When modeling these populations, it is essential to understand the limitations, assumptions, and implications of the models. The vast majority of previous adaptive therapy models use two distinct populations of treatment sensitive and treatment resistance cells[3]. Recent investigations have built upon this framework leading to discoveries in the cost of resistance in cancer, the importance of dose timing, and a number of parameters, which greatly improve the effectiveness of adaptive therapy regimens.

The concept of "cost of resistance" in tumor cells refers to the idea that the development of a drug-resistant phenotype may be associated with a fitness disadvantage for the cell in an environment without treatment[2,12,13]. In Gatenby's original model and most models since, the cost of resistance was used to motivate adaptive therapy[13]. Using a Lotka-Volterra competition model, Strobl and colleagues found that adaptive therapy can be very effective due to a resistance cost if the cell population is near its carrying capacity. However, it's important to note that resistance cost is highly variable and should never be considered absolute. If there is a resistance cost, the benefit thereof depends greatly on its relation to turnover rate[13]. Furthermore, in a spatially restricted model we may see a significant change in the benefit achieved from a resistant adaptation[13]. Therefore, while

cost of resistance depends greatly on carrying capacity and turnover, its presence or lack thereof should never be assumed.

In recent years, mathematical models have demonstrated that the timing of treatments plays a crucial role in achieving consistent and successful results. Kim et al. argues that adaptive therapy is most effective when it is tailored for the individual[15]. They found that TTP was increased significantly with intermittent therapy when the initial population of sensitive cells is large, and the sensitive cells impose a large competitive effect on resistant cells. Instead of stopping treatment at a 50% decrease in tumor burden, they found that stopping treatment at a 20% decrease in tumor burden was more effective[15]. This would even further reduce the burden of treatment a patient would endure. A separate model that allowed for phenotypic switching of resistance found that adaptive therapy was most effective when the re-sensitization rate of the resistant cell population to the sensitive population is high, and the growth rate of sensitive cells is low[15]. Therefore, by further understanding when adaptive therapy is most effective, treatments can be better personalized to the patient. Liu et al. propose a competitive differential model to determine therapeutic dose and timing in prostate cancer patients through a dynamic optimization problem. The model measures prostate specific antibodies (PSA) to determine the tumor burden and was fit to clinical trial data[16]. PSA dynamics have been shown to be a valuable tool for measuring prostate cancer burden, allowing for accurate prediction of patient response to treatment[17]. Additionally, this model identified self-renewal of prostate cancer stem cells as a potential driver of resistance to adaptive therapy[17]. After optimization, they found that their personalized treatment schedule used a lower dose, resulted in less resistant cells, and increased survival when compared to other common scheduling models[17].

One useful aspect of modeling evolutionary cancer dynamics is the identification of significant parameters that may greatly affect the efficacy of adaptive therapy. One such parameter is the number of rounds of cell division that must occur before a cell's DNA can acquire enough DNA damage to induce apoptosis[18]. This informed the conclusion that adaptive therapy algorithms that modulate treatment but never completely withdraw it are predicted to perform better under the realistic assumption that multiple cell divisions must occur before DNA damage causes apoptosis. This result was later verified *in vivo*[18].

A number of models have recently been published which are fitted to *in vitro* or *in vivo* adaptive therapy studies[18,19]. Despite the numerous adjustments and parameters explored in each subsequent model, they all converge on one central finding: adaptive therapy strategies hinder the development of therapeutic resistance and extend survival time using lower doses compared to maximum tolerated dose (MTD) approaches.

In silico Models

Compared to mathematical models, which represent relationships using differential equations and rely on a large number of assumptions, *in silico* (agent-based) models simulate complex interactions between individual cells (or agents) while accounting for spatial dynamics[21,22]. *In silico* models support adaptive therapy as an effective regimen to control emergence of resistance in tumors[2,6,22,23]. Recent research emphasizes the superiority of dose modulation over drug-vacation (intermittent and dose skipping) strategies and underscores the importance of tumoral heterogeneity and spatial structure as critical factors for accurately modeling adaptive therapy mechanisms.

Gallaher et al. utilized an off-lattice model which does not restrict cells to a confined grid[21] where space is the limiting factor and tumor subpopulations are well mixed[6]. More recently they used a similar approach to model the effect of adaptive therapy on metastatic tumors[23]. During a single cycle of adaptive therapy, which consists of a drug application period and a regrowth period, multiple parameters of the metastatic system can be identified, providing insights into tumor behavior. Cycle times are influenced by factors such as the number of metastases, tumor size, drug resistance, and cell turnover rate, with larger tumors and more resistance leading to longer cycles[23]. The cycle dynamics can reveal variations between metastases in terms of size and phenotype, potentially indicating differences associated with the primary tumor's Gleason score[23]. Thomas et al. used the Hybrid Automata Library(HAL) modeling framework to simulate the best method for two drug administration and how various spatial constraints affect adaptive therapy protocols (*Fig 3.*)[22]. Dose modulation protocols improved time to progression compared to standard treatment, with ping-pong protocols showing long-term tumor control while using less drug[22]. The efficacy of adaptive therapy hinged on elements such as the fitness cost of resistance, cell turnover, and the probability of a dividing cell replacing its neighbor[22]. Strobl et al. demonstrated the importance of spatial dynamics with a two dimensional on-lattice model which was contrasted with a mathematical model and fit to clinical prostate cancer data[2]. This study found that the spatial organization of resistant tumor cell populations is a crucial factor in cancer treatment, with adaptive therapy being most effective when resistance is clustered in a single location[2]. The research supports the need for patient-specific, adaptive therapy protocols that consider not only tumor evolution but also its ecology[2]. In 2020, The Cancer Adaptive Therapy Models (CATMo) conference

assembled researchers interested in models of adaptive therapy. From this conference came the paper from West et al. in which the researchers gave their perspectives on linking mathematical and computational models to clinical settings[3].

Recently, dose modulation (*Fig. 3d-f*) has been identified as a much more effective alternative to the fixed dose drug-vacation protocol. In dose modulation, less drug is given to a responding tumor and more to a rebounding tumor[6] but never stops as it does in drug-vacations. Dose modulation has been found to perform better with decreasing amounts of drug[22]. However, it has been posited that more invasive tumors respond better to drug-vacation protocols[6]. A two-drug approach will optimize dose modulation especially when using a ping-pong on progression approach where the drug is switched when the tumor begins to progress[22].

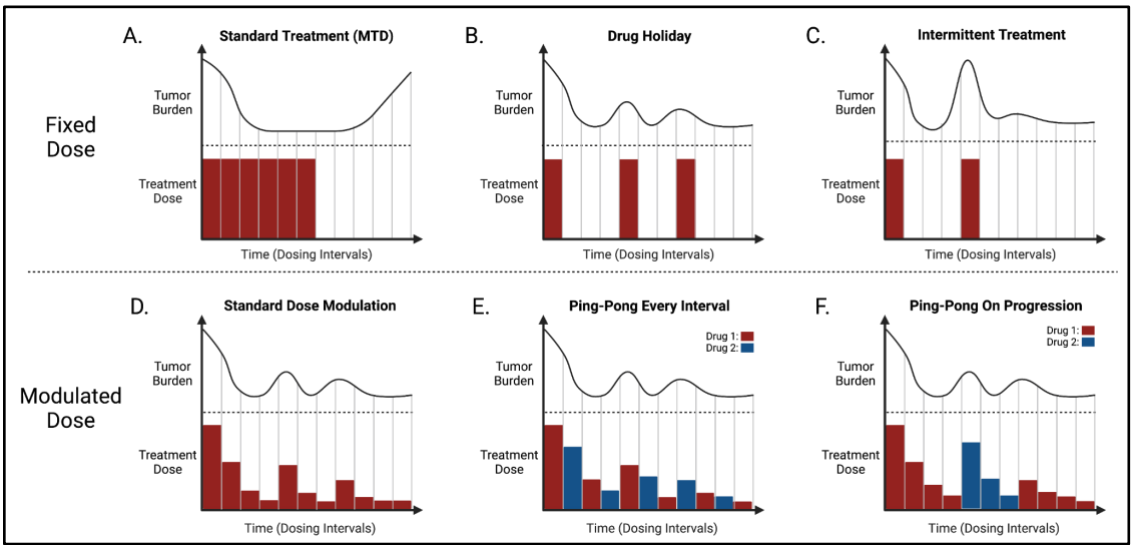

Figure 3. Illustration Of Various Adaptive Therapy Regimens Adapted From Thomas Et Al., comparing treatment dose to tumor burden over time. (a) Standard maximum tolerated dose: continuous treatment until remission is achieved. (b) Drug holiday: treatment is stopped upon response and resumed upon progression. (c) Intermittent treatment: treatment is restarted when the tumor progresses to its original level. (d) Standard dose modulation: dose amount is adjusted based on tumor response. (e) Ping-pong every interval: dose amount is adjusted, and the drug is alternated at each dosing interval. (f) Ping-pong on progression: dose amount is adjusted, and the drug is changed once the tumor begins to progress. Note that strategies (a-d) may employ a two-drug regimen (cocktail, every interval, or on progression), while strategies (e-f) exclusively use two-drug regimens.

As previously mentioned, spatial structure is an essential factor in cell dynamics that is challenging to interpret in mathematical models. Spatial constraints alter how a cell population develops resistance due to competition for space[22] and drug perfusion[6]. Spatial constraints may further support modulated dosing as decreasing dose causes resistant clones to be restrained in the center of bacterial colonies[2]. It is important to note, however, that none of these models provide a realistic representation of drug delivery through the circulatory system. They either impose the drug evenly across space or have it diffused from the outside, which may not accurately reflect real-world scenarios.

Intra-tumoral heterogeneity is identified as a possible biomarker target for predicting patient response to adaptive therapy[22]. In the metastatic model, the most important parameter for resistance was inter-tumoral heterogeneity, which greatly affects tumor size distributions as different cell compositions will respond to treatment at different rates[23]. One limitation of these models is that they are all 2D, and the effects of spatial constraints might change in 3D. Future studies should consider developing 3D models to better understand the role of spatial constraints in cell dynamics and response to treatment.

CHAPTER 3

PRECLINICAL STUDIES

In vitro Studies

Bacevic et al. conducted an in-vitro study investigating the effectiveness of adaptive therapy using CDK inhibitors for cancer treatment. CDK inhibitors are a class of targeted therapies that aim to disrupt the uncontrolled cell division in cancer by interfering with cyclin-dependent kinases (CDKs), proteins that play a crucial role in regulating the cell cycle[30]. The study focused on determining whether drug resistance truly comes with a cost and if sensitive cells are capable of suppressing resistant cells' proliferation. The study provided substantial evidence that resistant cells experienced diminished fitness, which was intensified by spatially structured tumor growth. Consequently, lower drug doses proved more effective in managing tumor burden and resistance. The in-vitro findings were also replicated *in silico*, and the study indicated that the fitness cost of resistance might be further amplified *in vivo*. This research highlights the potential of AT as an evolutionarily grounded approach to enhance cancer treatment outcomes by leveraging the inherent fitness penalties of resistant cells and their context-dependent sensitivities[30].

In Vivo Studies

A number of studies have been conducted on preclinical models of ovarian and breast cancer. Robert Gatenby et al tested the effectiveness of metronomic therapy, using smaller drug doses in shorter, regular intervals or continuously to reduce toxicity and increase the antiangiogenic effects, through treating severely immunodeficient mice with

an ovarian cancer tumor cell line with traditional chemotherapy[5]. Their initial experiment was able to confirm that therapy could be modulated in a way that allows persistence of a small stable tumor[5]. However, some obvious limitations were apparent because modest tumor growth in the adaptive therapy animals did occur[5]. They repeated the experiment again by changing the intensity of the therapy applied based on the tumor size[5]. In both experiments, tumor volume stability could be enforced by a modulated treatment strategy[5]. In both cases, the amount of drug necessary to maintain tumor stability decreased substantially with time so that at the completion of the experiment, control was achieved with administration of 10 mg/kg of carboplatin[3].

A follow-up study conducted by Enriquez-Navas et al. tested adaptive strategy on human triple negative and a less aggressive estrogen receptor-positive (ER+) breast cancer cell lines engrafted into immunodeficient mice. Two algorithms were tested including dose modulation and dose skipping. The results showed that adaptive therapy protocols, particularly the dose modulation protocol, was able to increase survival significantly. In contrast, dose skipping was not effective in most cases[10]. In this experiment, tumor burden was monitored using magnetic resonance imaging (MRI). In 60-80% of mice under adaptive strategies, stable control of the tumor burden was achieved following the initial reduction in tumor size. One potential explanation for the reduction in dose needed to control the tumor, as suggested by the researchers, was that adaptive therapy normalized perfusion of the tumor, potentially increasing the efficiency of drug delivery. Overall, this study demonstrated that adaptive therapy, as an evolutionarily based strategy, could prolong progression-free survival in both breast cancer preclinical models compared to standard therapy[10].

This experiment was on hormone sensitive cell lines, however, to have more realistic results, Seyedi et al. conducted another preclinical experiment (in preparation [2023]) using the same ER+ cell line (MCF7) that was selected to be resistant to standard hormone therapy (Fulvestrant) as well as a common therapy that targets CDK4/6 (Palbociclib) in NSG (immunodeficient) mice. They have tested two chemotherapy drugs, capecitabine and gemcitabine in both single drug and multi drug therapies. In this study they also used dose modulation and intermittent protocols, and in a combination strategy, drugs have been administered in two methods, 1. Tandem (apply both drugs at the same time); 2. Ping-pong (change the drug every 3 days). In both single and multi-drug therapies, the dose modulation protocols worked better compared to MTD and intermittent therapy in prolonging overall survival. Surprisingly, the tumors often remained stable at small sizes even after therapy had been withdrawn for several weeks[11].

CHAPTER 4

CLINICAL TRIALS

The introduction of adaptive therapy from Robert A. Gatenby in 2009 proposed a new perspective in the field of oncology. With the study came the viewpoint that eradication may be a misguided goal of cancer therapy, but taking control and stabilizing tumor size might be more effective[5]. As stated by Gatenby et al. (2009) adaptive therapy did not always have the most promising results. The initial simulations showed that the tumor size was progressing whereas the maximum tolerated dose therapy was eradicating tumor cells, yet as time progressed, the results of the study showed that when applied, adaptive therapy increased survival rate and tumor control[5].

A recent pilot clinical trial was composed of a small cohort of metastatic castrate-resistant prostate cancer patients to receive dose skipping treatment[25]. Abiraterone was administered to patients until a 50% drop of the prostate-specific antigen biomarker was achieved[25]. Treatment was then stopped until the evidence of tumor burden returned to pre-treatment levels before being restarted[25]. When compared to patients receiving standard care, trial participants were able to receive a lower cumulative drug dose and cancer-progression[25]. Some drawbacks of the study were the small sample size of the cohort and absence of a randomized control group, which is being rectified in the phase II clinical trial.

Since this original study, a number of new clinical trials have begun to take place (NCT05393791, NCT05080556, NCT4872608, NCT4388839, NCT3511196); as of recently, these clinical trials have not been completed[25]. With large clinical trials operating

interdependently with mathematical and computational models, adaptive therapy is making significant headway in the pursuit to control cancer progression.

Advancements have been made in cancer adaptive therapy with the two dose-scheduling protocols being cataloged into two types, dose modulation (when the dose is increased or decreased at regular intervals based on tumor response) and dose skipping (when a high dose is administered followed by a drug holiday and repeated) with the latter being translated into the clinic[25]. Challenges with opportunities for growth in translating adaptive therapy to clinical trials would be identifying the correct mathematical model to utilize for patient treatment, identifying when it would be correct to use adaptive therapy treatment versus standard treatment, and optimizing the dose administration protocol[25].

Researchers at Leiden University Medical Center are studying Patient-specific Adaptive vs. Continuous Abiraterone treatment with 168 participants with castrate-resistant prostate cancer[25,26]. Researchers will have patients take abiraterone or enzalutamide daily with the prostate-specific antigen biomarker being measured every month. Once the biomarker has dropped below 50%, treatment will pause until it rises above pretreatment baseline. If patient death or cancer progression occurs, then the treatment will be considered a failure. The estimated completion date of the trial is November 2027[26].

CHAPTER 5

DISCUSSION

Applications In Immunotherapy and The Microbiome

To further explore the possibility of conquering drug resistance, upcoming research should examine the efficacy of combining adaptive therapies with immunotherapies and the microbiome. While adaptive therapy has shown promise in treating drug-resistant cancers, its implementation with immunotherapies poses unique challenges due to the difficulty in titrating the immune system, a binary system. Recent research has investigated the ability of the immune system to recognize drug-resistant cells and how combining targeted therapies with immunotherapies can suppress tumor evolution and limit the emergence of drug resistance.

Bardelli et al. tested the ability of the immune system to recognize drug-resistant cells by testing syngeneic mouse models of colorectal cancer sensitive to targeted therapies[26]. By combining targeted therapies with immunotherapies, the researchers aimed to suppress tumor evolution and limit the emergence of drug resistance, thus leading to long-term responses They found that this manipulation of mutational loads can improve therapeutic responses to the cancer cells that were available with targeted drugs alone[26]. Rationally combined targeted and immunotherapies can restrain tumor evolution and can limit the emergence of drug resistance, thus leading to long-term responses[10].

As an example of resistance to immunotherapy and how to prevent it, consider the majority of patients with metastatic melanoma who initially respond to anti-PD therapy but eventually relapse over time. Similar resistance and relapse have been observed in lung

cancer[28]. In the referenced study, it is suggested that using radioisotope labeled PD1 variants or anti-PDL1 monoclonal antibodies could potentially enhance the monitoring and measurement of PDL1 expression through *in vivo* imaging, covering a larger area of the tumor. Furthermore, assessing additional co-inhibitory and co-stimulatory molecules is crucial to comprehend the efficacy of the immune response. Ultimately, these factors may prove to be vital in understanding primary resistance to anti-PD therapy[28].

Cancer-protective microbes have been linked to cancer-fighting mechanisms such as reducing tumor size, inhibiting cancer cell proliferation, and preventing tumor formation. These microbes typically work by enhancing the individual's immune system to improve anti-cancer mechanisms and responses[28]. Cancer-protective microbes may play a critical role in enhancing adaptive therapy and improving treatment outcomes.

Critiques

In this section, we will critically evaluate the methodologies used in the paper to study adaptive therapy. The efficacy of adaptive therapy as a treatment regimen heavily depends on the reliability of the methodologies used to study and implement it. The studies use a range of methodologies, including mathematical modeling, *in silico* modeling, *in vivo* and *in vitro* studies, and clinical trials. Evaluating the strengths and limitations of each methodology can deepen our understanding of the reliability and effectiveness of the results presented in the paper, as well as identify areas for future research.

Most of the mathematical models use the Lotka-Volterra framework, which was originally designed for predator-prey interactions in ecology but has become the foundation of modern mathematical oncology models. While these models are effective in calculating

two population interactions over time, they are restricted to two dimensions and a relatively low number of parameters compared to *in silico* models. Although restricting a model to a certain number of interactions is important to understand the underlying mechanisms, a lack of spatial dynamics is a crucial factor in evolutionary cancer dynamics. Therefore, mathematical models have their limitations in accurately modeling adaptive therapy mechanisms.

In silico models incorporate three-dimensional spatial dynamics and allow for simultaneous, scalable simulations of multiple cell types. However, these simulations are algorithmically demanding and limited by the computational hardware. Another common critique of agent-based models is that they include a high number of parameters, making it difficult to pinpoint which factors are responsible for the observed results. It is worth noting that no three-dimensional model has been studied in adaptive therapy.

In vitro studies are often criticized for lacking a three-dimensional framework, but the reviewed organoid model does allow for three-dimensional spatial dynamics. However, *in vitro* studies do not model tumor interactions within a host, which is an important aspect of cancer research. *In vivo* models, although challenging in execution, exhibit the most accurate results in human clinical trials. However, the reviewed studies have only utilized immunocompromised mice, and we do not know how an intact immune system plays a role in adaptive therapy *in vivo*. It is also important to note that in the mouse experiments and the pilot clinical trial, the researchers did not measure the sensitive and resistant cell populations to verify that they are behaving as the models predict. Additionally, only the pilot clinical trial involved a host with an intact immune system. With low doses of chemo

in adaptive therapy, there is hope that we may preserve and benefit from the immune system.

Human clinical trials are the most crucial measure of any treatment regimen, but they come with their own set of limitations. Clinical trials must focus on a specific cohort of patients to develop accurate results, which often leads to small sample sizes, such as in the pilot clinical trial. As cancer is an incredibly dynamic and heterogeneous entity, results from these studies can be misleading. Moreover, tumors exhibit vastly different phenotypes that can alter treatment response even within cancer types. Moving forward, it is essential to understand how the patient cohort, treatment mechanism, and adaptive therapy protocol tie into the results of clinical trials to assess adaptive therapy accurately as a cancer treatment regimen.

CONCLUSION

Adaptive therapy, a novel approach to cancer treatment that uses reduced doses of drugs to inhibit the development of drug-resistant cells, has shown promising results in preclinical and early-stage clinical trials. The use of mathematical modeling and *in silico* modeling has demonstrated the effectiveness of adaptive therapy in controlling the emergence of resistance in cancer cells, with critical factors including spatial structure and tumor heterogeneity. Moreover, preclinical studies have shown that adaptive therapy can prolong progression-free survival in ovarian and breast cancer models, with lower drug doses and dose modulation protocols proving more effective. The convergence of similarly successful demonstrations of effective tumor control across the studies we evaluated highlights adaptive therapy as a promising clinical strategy in oncology.

Although ongoing debate exists regarding the effectiveness of adaptive therapy in comparison to other more aggressive treatment approaches, maintaining tumor volume through adaptive therapy has been shown to lead to less growth of resistant phenotypes. Moreover, initial modeling has indicated that an adaptive therapy regime can induce longer survival, even when the tumor is slowly increasing over a long period of time. Challenges in translating adaptive therapy to clinical trials include identifying the correct mathematical model, knowing when to use adaptive therapy treatment versus standard treatment, and optimizing the dose administration protocol. The role of the microbiome in enhancing adaptive therapy treatments also requires further exploration.

Overall, the use of multiple methodologies, including mathematical modeling, *in silico* modeling, *in vivo* and *in vitro* studies, and clinical trials, has demonstrated the potential of adaptive therapy as a personalized approach to cancer treatment. Further

research is necessary to determine the optimal application of adaptive therapy for different types of cancer and to better understand the physical implications of ongoing monitoring and treatment. The convergence of successful results across multiple studies, however, highlights the potential for adaptive therapy as a promising clinical strategy in oncology.

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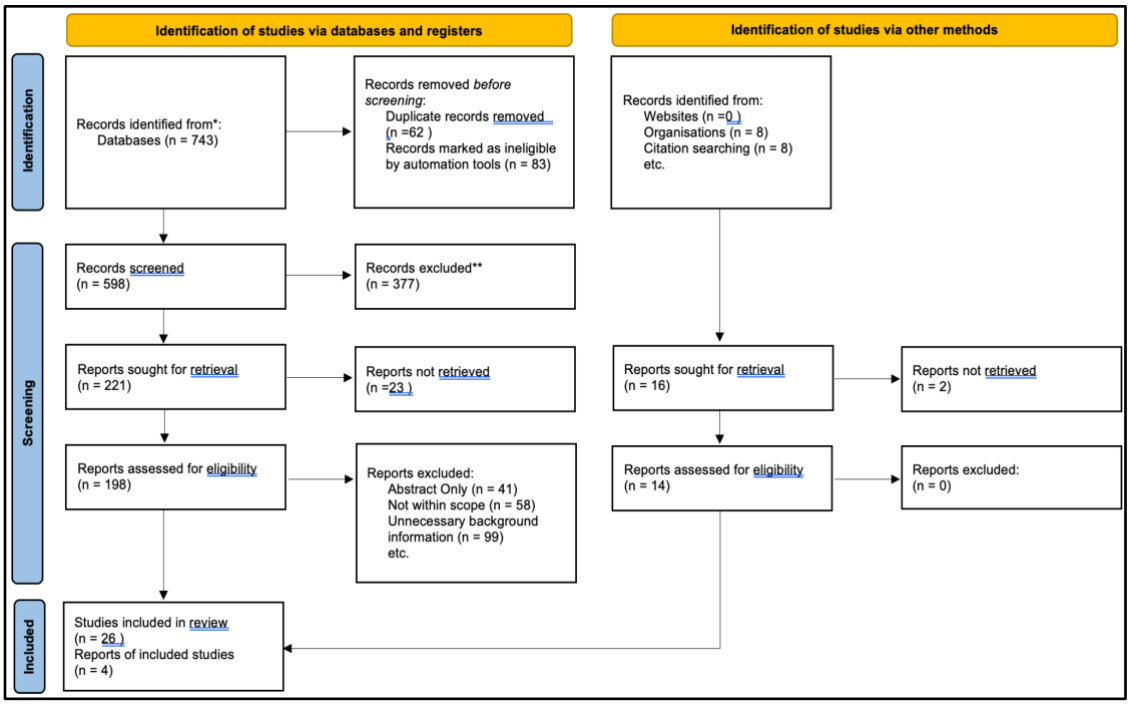
APPENDIX A

PRISMA 2020 FLOW DIAGRAM FOR NEW SYSTEMATIC REVIEWS



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