Neoadjuvant Therapy in Non-Small Cell Lung Cancer: A Survey

Abstract

Neoadjuvant therapy for non-small cell lung cancer (NSCLC) involves administering treatments such as chemotherapy and immunotherapy prior to surgical intervention to shrink tumors and enhance surgical outcomes. This survey paper provides a comprehensive analysis of the current landscape of neoadjuvant therapy, emphasizing the integration of immune checkpoint inhibitors (ICIs) and chemotherapy to address tumor heterogeneity and resistance challenges. Despite advancements, chemotherapy resistance remains a significant barrier, necessitating ongoing research into molecular mechanisms and innovative treatment strategies. The paper highlights the role of predictive modeling and advanced diagnostic technologies in optimizing treatment regimens, underscoring the importance of personalized treatment plans that leverage molecular profiling and biomarkers. The impact of intra-tumor heterogeneity and treatment timing on surgical decision-making is explored, with a focus on radiomic analysis and multidisciplinary approaches to improve patient outcomes. Recent advancements, including the development of targeted nanoconjugate platforms and novel imaging techniques, are discussed as promising avenues for enhancing therapeutic efficacy. The survey concludes by advocating for continued innovation and collaboration across disciplines to refine neoadjuvant therapy practices and improve prognosis for NSCLC patients.

1 Introduction

1.1 Overview of Neoadjuvant Therapy

Neoadjuvant therapy is crucial in treating non-small cell lung cancer (NSCLC), aimed at optimizing tumor control and enhancing patient outcomes prior to surgical intervention. This approach reduces tumor size and addresses micrometastatic disease, thereby facilitating surgical resection and improving long-term survival rates. By identifying early responders, neoadjuvant therapy enables tailored treatment strategies that maximize therapeutic efficacy [1].

The advent of chemotherapy and immunotherapy, particularly immune checkpoint inhibitors (ICIs), has significantly reshaped the neoadjuvant treatment landscape. These therapies seek to establish durable effects by modulating the immune system to recognize and eliminate cancer cells, thereby improving overall survival and pathologic complete response rates in patients with resectable lung cancer [2]. Nevertheless, challenges such as chemotherapy resistance and tumor heterogeneity persist, highlighting the need for ongoing research to refine therapeutic options [2].

The importance of neoadjuvant therapy in NSCLC is underscored by its potential to improve surgical outcomes and patient survival, necessitating continuous innovation and multidisciplinary approaches. As research progresses, the development of predictive models and advanced diagnostic technologies will enhance the precision and effectiveness of neoadjuvant therapies, ultimately contributing to improved patient care and treatment outcomes [3].

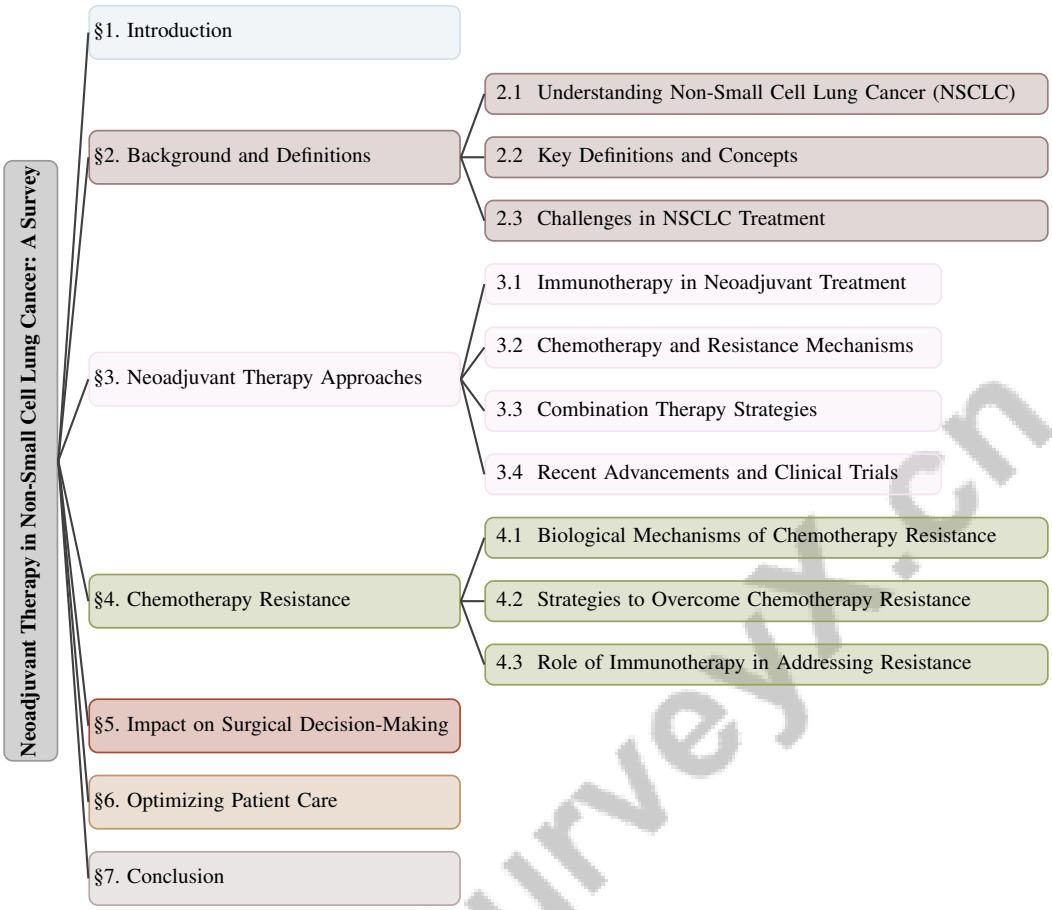


Figure 1: chapter structure

1.2 Rationale for Treatment Selection

The selection of neoadjuvant treatments for NSCLC involves a complex decision-making process that incorporates tumor biology, patient-specific factors, and the limitations of conventional therapies. The limited effectiveness and high toxicity of existing chemotherapy regimens necessitate exploring more effective alternatives [2]. Immunotherapy, particularly through ICIs, shows promise in enhancing anti-tumor responses by modulating the immune system. However, adaptive immune resistance, where tumors evade detection, underscores the need for strategies to improve immunotherapy efficacy [4].

Combining chemotherapy with immunotherapy aims to exploit their synergistic effects, controlling tumor growth while minimizing damage to healthy cells [5]. This dual approach is particularly beneficial in addressing tumor heterogeneity, a key factor influencing treatment outcomes [6]. Additionally, the timing of radiation doses significantly impacts immunotherapy efficacy, emphasizing the importance of precise treatment scheduling [3].

Patient health and tumor characteristics are essential in determining appropriate neoadjuvant therapy [6]. Developing standardized benchmarks for assessing pathologic response is crucial for evaluating therapeutic efficacy and guiding clinical decisions, thereby enhancing the success probability in clinical trials [7]. Advanced diagnostic technologies can further aid in identifying responders early, optimizing treatment regimens, and improving patient prognosis [2].

1.3 Structure of the Survey

This survey on neoadjuvant therapy for NSCLC is structured to provide a comprehensive exploration of the topic. The introduction establishes the significance of neoadjuvant therapy and its role in optimizing surgical outcomes, highlighting its objectives and the rationale for treatment selection,

including the integration of chemotherapy and immunotherapy to address tumor heterogeneity and resistance challenges.

The second section, "Background and Definitions," delves into the epidemiological and clinical aspects of NSCLC, defining key concepts such as neoadjuvant therapy, immunotherapy, chemotherapy, and chemotherapy resistance, while discussing the critical role of surgical decision-making in the treatment process.

The third section, "Neoadjuvant Therapy Approaches," examines various therapeutic strategies, emphasizing the roles of immunotherapy and chemotherapy. It compares their mechanisms, benefits, limitations, and reviews recent advancements and clinical trials that have shaped current practices.

The fourth section, "Chemotherapy Resistance," explores the biological mechanisms underlying chemotherapy resistance in NSCLC and reviews strategies to overcome these challenges, considering the potential role of immunotherapy in addressing resistance [4].

In the fifth section, "Impact on Surgical Decision-Making," the survey assesses how neoadjuvant therapy influences surgical planning and patient prognosis, factoring in intra-tumor heterogeneity and treatment timing [6].

The sixth section, "Optimizing Patient Care," discusses strategies for personalizing treatment plans through biomarkers, molecular profiling, and multidisciplinary approaches, aiming to enhance the precision and effectiveness of neoadjuvant therapies [7].

Finally, the "Conclusion" summarizes the survey's findings and reflects on future research and clinical practice directions, emphasizing the importance of continued innovation and collaboration to improve patient outcomes [3].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Understanding Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, significantly impacting lung cancer mortality [8, 9]. This prevalence underscores the necessity for effective management strategies, given its profound public health implications. NSCLC is characterized by heterogeneity, complicating treatment due to variations in disease physiology, clinical data, genomics, and responses, which challenge survival predictions. The primary histological subtypes, lung adenocarcinoma (L-ADCA) and lung squamous cell carcinoma (L-SCCA), exhibit distinct histopathological and molecular features [10].

NSCLC's impact on patient survival and quality of life is significant. The heterogeneity of the patient population and variability in treatment responses present challenges, particularly in managing stage III NSCLC [11]. Prognosis prediction is complex, necessitating a unified analytic framework for enhanced accuracy [12]. Advancements in radiomics facilitate feature extraction from clinical CT scans, improving treatment response and outcome predictions [13]. Clinical trial data integration has provided insights into neoadjuvant therapies, combining systemic and surgical interventions to enhance outcomes.

NSCLC's complexity demands comprehensive diagnostic and treatment approaches, leveraging advancements in radiomics, surgical techniques, and algorithmic decision-making to optimize outcomes. Establishing links between radiological features and genomic or molecular expressions remains a critical challenge [10]. This survey reviews NSCLC treatment modalities, including chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy [6]. A multidisciplinary approach is essential to address tumor heterogeneity and enhance therapeutic precision.

2.2 Key Definitions and Concepts

In neoadjuvant therapy for NSCLC, key terms are vital for understanding the therapeutic landscape. Immunotherapy, a crucial strategy, enhances the immune system's capacity to detect and eradicate cancer cells, primarily through immune checkpoint inhibitors, transforming treatment paradigms despite challenges in predicting responses due to complex genomic profiles. Antiangiogenic therapy aims to normalize tumor vasculature, improving immunotherapy outcomes [14].

Chemotherapy uses cytotoxic agents targeting rapidly dividing cells. While effective in tumor reduction, it is limited by non-specific toxicity and resistance mechanisms [15]. Platinum-based chemotherapies, such as cisplatin, are significant, though resistance development impairs efficacy [16]. Understanding resistance mechanisms, such as the relationship between ER stress and chemotherapy resistance, is crucial for enhancing efficacy [17].

Chemotherapy resistance is a formidable challenge, as tumors develop mechanisms to evade drug effects, leading to treatment failure. This necessitates innovative approaches to overcome resistance and improve outcomes. Variability in biomarker robustness, particularly in radiomic features, requires careful evaluation for accurate predictions and effective planning [13].

Key terms such as progression-free survival (PFS) and overall survival (OS) are essential for evaluating neoadjuvant therapy outcomes [18]. Statistical concepts like the cure mixture model and nonproportional hazards are relevant for understanding long-term effects in patients undergoing therapy [19]. Causal inference, estimand framework, target trial framework, and observational data are significant in NSCLC, providing structured approaches to understanding treatment effects [20].

Comprehensive understanding of definitions and concepts related to neoadjuvant therapy in NSCLC is crucial for advancing treatment strategies. This knowledge fosters personalized therapeutic approaches addressing tumor heterogeneity and resistance complexities. By integrating insights from advancements in targeted therapies, multimodal treatment options, and molecular characteristics, clinicians can optimize outcomes and enhance survival rates in this diverse population [21, 9, 22, 11, 23].

2.3 Challenges in NSCLC Treatment

Treating NSCLC presents numerous challenges due to tumor heterogeneity and rapid resistance development. Tumor heterogeneity, with diverse genetic and phenotypic profiles, impacts treatment efficacy as varying cell populations respond differently. Designing effective regimens is complicated by the dynamic evolution of tumor cells under therapeutic pressure, leading to suboptimal outcomes. Factors like the immunosuppressive tumor microenvironment, immune-modulating effects of therapies, and therapy-related toxicities further complicate strategies. Incorporating these variables into mathematical and computational models is essential for guiding rational therapy design and improving outcomes [24, 25].

A critical challenge is the high incidence of intrinsic and acquired drug resistance, diminishing chemotherapy and immunotherapy effectiveness [26]. Mechanisms like drug efflux, cellular stemness, and microenvironment interactions enable cancer cells to evade effects. Notably, calcium channels like Orai3 mediate chemoresistance to cisplatin through signaling pathways, complicating the landscape [27].

NSCLC's complexity is further underscored by challenges in analyzing high-dimensional datasets, crucial for predictive model development and deep learning applications in precision medicine [12]. Limited availability of comprehensive datasets increases overfitting risks, hindering progress. Reliance on labeled data and lack of feature generalizability also hampers effective survival prediction [12].

Effective treatment delivery is obstructed by the tumor microenvironment, complicating autoimmune side effects management and patient response predictions. Current methodologies, particularly in immunotherapy, struggle with late-onset responses and the necessity for multiple endpoints in trials, highlighting the need for innovative trial designs and analytical approaches [6].

Addressing NSCLC treatment challenges requires a comprehensive strategy, combining personalized medicine advancements with genomic and phenotypic data and innovative trial designs. This multifaceted approach aims to optimize outcomes by leveraging multimodal data integration, including radiological, pathological, and genomic information. Such integration is vital for developing next-generation biomarkers and refining therapeutic decision-making, enhancing targeted therapies and immunotherapies tailored to individual profiles [22, 28, 21, 23].

In recent years, the treatment landscape for non-small cell lung cancer (NSCLC) has evolved significantly, with neoadjuvant therapy emerging as a pivotal approach in enhancing patient outcomes. This evolution is underscored by a variety of strategies, including immunotherapy, chemotherapy, and combination therapies. To better understand these approaches, Figure 2 illustrates the hierarchical

structure of neoadjuvant therapy for NSCLC, highlighting key strategies in these treatment modalities. The figure emphasizes the integration of immune checkpoint inhibitors, the role of the tumor microenvironment, resistance mechanisms, and advanced computational methods, all of which are crucial for optimizing treatment efficacy. By examining these elements, we can gain insights into the complexities of NSCLC treatment and the potential pathways for future research and clinical application.

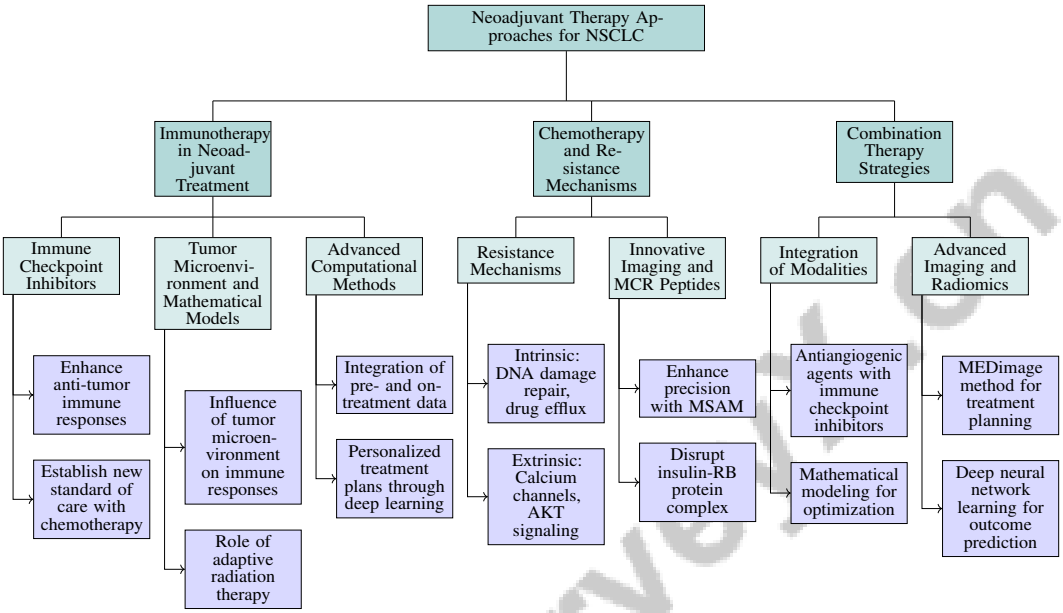


Figure 2: This figure illustrates the hierarchical structure of neoadjuvant therapy approaches for NSCLC, highlighting key strategies in immunotherapy, chemotherapy, and combination therapies. It emphasizes the integration of immune checkpoint inhibitors, the role of tumor microenvironment, resistance mechanisms, and advanced computational methods in optimizing treatment efficacy.

3 Neoadjuvant Therapy Approaches

3.1 Immunotherapy in Neoadjuvant Treatment

Immunotherapy has revolutionized neoadjuvant treatment for NSCLC by harnessing the immune system to target cancer cells, significantly advancing therapeutic strategies [6]. Central to this approach are immune checkpoint inhibitors (ICIs), which enhance anti-tumor immune responses by inhibiting pathways that suppress T cell activation [4]. The integration of ICIs with chemotherapy has established a new standard of care for selected NSCLC patients, enhancing therapeutic efficacy.

The success of immunotherapy is intricately linked to its interaction with the tumor microenvironment, which profoundly affects immune responses. Mathematical models, such as those by Xing et al., emphasize the role of adaptive radiation therapy in optimizing immune responses and treatment outcomes [3]. These models are crucial for understanding tumor-immune dynamics, thereby refining immunotherapeutic strategies.

Advanced computational methods, including deep learning architectures, have further enhanced the application of immunotherapy in NSCLC by integrating pre- and on-treatment data for improved survival predictions [29]. These methodologies facilitate the identification of radiomic features predicting tumor responses, enabling personalized treatment plans. Hybrid models that combine machine learning with domain-specific knowledge offer innovative solutions to the complexities of immunotherapy.

Despite these advancements, challenges remain in predicting patient responses due to intricate genomic profiles and variable tumor behaviors. Current initiatives aim to utilize deep neural networks to integrate mutation and expression profiles, transforming pharmacogenomic insights into actionable

strategies for personalized treatment. A sophisticated model trained on a diverse dataset of 622 cancer cell lines predicts IC50 values for 265 anti-cancer drugs, achieving a mean squared error of 1.96 in log-scale IC50 values. This model has been applied to assess drug responses across 9,059 tumors spanning 33 cancer types, identifying effective treatments like EGFR inhibitors for NSCLC and uncovering novel therapeutic targets. Such analyses enhance drug response predictions and illuminate molecular mechanisms of drug resistance, potentially leading to innovative oncology treatments [1, 30]. Understanding delayed survival benefits linked to immunotherapy, often overlooked in traditional clinical trials, has spurred the development of novel trial methodologies.

3.2 Chemotherapy and Resistance Mechanisms

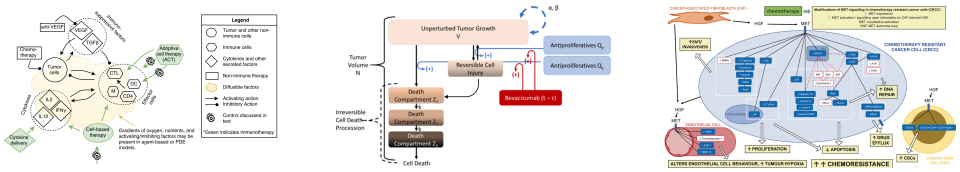
Chemotherapy remains a cornerstone of neoadjuvant treatment for NSCLC, aimed at reducing tumor burden to improve surgical outcomes. However, its efficacy is often hindered by the complex interplay of oncogenic pathways and diverse genetic backgrounds, resulting in heterogeneous treatment responses [2]. The non-specific nature of chemotherapy can adversely affect healthy cells, while cancer cells frequently develop resistance mechanisms that undermine therapeutic efficacy [27].

Resistance to chemotherapy in NSCLC arises from intrinsic and extrinsic mechanisms. Intrinsic resistance is characterized by enhanced DNA damage repair and drug efflux via membrane transport systems, which diminish the cytotoxic effects of agents like cisplatin. The involvement of calcium channels, such as Orai3, and the AKT signaling pathway further complicates our understanding of chemoresistance [27]. Additionally, the presence of nonproportional hazards (NPH) between treatment groups, especially when comparing immunotherapy and chemotherapy, complicates the assessment of treatment efficacy [31].

Recent research has categorized studies into chemotherapy drugs and natural compounds, proposing frameworks for combining these approaches to enhance treatment efficacy [2]. MET-driven chemoresistance significantly impacts cancer stem cells and tumor microenvironments under hypoxic conditions, complicating treatment outcomes. Moreover, non-coding RNAs, such as AFAP1-AS1 and miR-139-5p, have been implicated in mediating resistance in NSCLC, presenting potential therapeutic intervention avenues [2].

Innovative imaging techniques, such as the Multimodal Spatial Attention Module (MSAM), have been developed to enhance chemotherapy precision by emphasizing tumor-related regions in PET images, thus minimizing effects on normal tissues. The application of MCR peptides to disrupt the insulin-retinoblastoma (RB) protein complex restores RB's tumor suppressor function, offering a promising strategy to overcome chemoresistance. Findings indicate that MCR peptides, particularly MCR10, effectively interfere with the insulin-RB complex formation in various human cancer cell lines, potentially enhancing existing therapies and addressing the challenge of drug resistance [32, 26].

The inadequate effectiveness of current first-line treatments, particularly in late-stage NSCLC, highlights the urgent need for strategies to overcome resistance and improve survival rates. A comprehensive understanding of the molecular mechanisms contributing to intrinsic and acquired resistance is essential for developing targeted therapies to enhance chemotherapy efficacy in neoadjuvant settings. Strategies may involve combinational and personalized therapies that consider specific resistance pathways, including ATP transport mechanisms and receptor tyrosine kinases like MET, implicated in promoting resistance to both cytotoxic and targeted therapies [16, 26, 33, 34].



(a) Cell-based therapy and immunotherapy in cancer treatment[24]

(b) Model of Tumor Growth and Cell Death[28]

(c) Chemotherapy-Resistant Cancer Cell Metastasis and Chemoresistance[33]

Figure 3: Examples of Chemotherapy and Resistance Mechanisms

As illustrated in Figure 3, neoadjuvant therapy, particularly chemotherapy, is crucial for cancer treatment, aiming to reduce tumor size before surgery. However, resistance mechanisms developed by cancer cells pose significant challenges. The first diagram emphasizes cell-based therapy and immunotherapy, detailing tumor-immune cell interactions and involved pathways, such as anti-VEGF. The second diagram presents a mathematical model of tumor growth and cell death, highlighting tumor volume dynamics and antiproliferative drug effects. The third diagram explores chemotherapy-resistant cancer cell metastasis and chemoresistance, depicting the complex network of cellular components and pathways contributing to resistance. Together, these visual representations underscore the multifaceted nature of cancer treatment and the ongoing challenges of chemoresistance, necessitating continued research and innovation in therapeutic strategies [24, 28, 33].

3.3 Combination Therapy Strategies

Combination therapy strategies in NSCLC aim to enhance treatment efficacy by integrating multiple modalities to address the complex biology of tumors. A promising approach involves combining antiangiogenic agents with immune checkpoint inhibitors to normalize tumor vasculature, improving immune cell infiltration and overall immunotherapy effectiveness [14]. This integration targets NSCLC's metabolic vulnerabilities, offering potential for improved therapeutic outcomes [35].

Mathematical modeling is vital for optimizing combination therapy designs. Models that quantitatively represent interactions among tumor cells, immune cells, and therapies provide insights into optimal treatment scheduling and combination strategies. These models enable the construction of ordinary differential equations simulating tumor-immune interactions, facilitating the development of optimized treatment plans [36]. Furthermore, integrating global sensitivity analysis with machine learning techniques refines drug delivery strategies, particularly for mixed therapies, enhancing treatment precision [37].

Therapeutic scheduling is critical in combination therapy. For instance, administering bevacizumab before combination antiproliferatives can maximize efficacy by exploiting temporal drug action dynamics [28]. Targeting specific genetic mutations, such as those in the RAS family, can also be strategically combined with other therapies to address NSCLC's molecular drivers [21].

Advanced imaging and radiomics contribute significantly to developing combination therapy strategies. The MEDimage method integrates radiomic features with clinical decision-making, demonstrating how imaging data can inform treatment planning and enhance combination therapy effectiveness [38]. Moreover, a systematic study on deep neural network learning from whole slide images has underscored the importance of considering varying resolutions and field-of-views in predicting treatment outcomes, thus informing combination therapy designs [39].

The exploration of combination therapy strategies in NSCLC increasingly relies on an interdisciplinary approach that integrates mathematical modeling, advanced imaging techniques, and strategic scheduling. This comprehensive methodology addresses tumor heterogeneity and treatment resistance complexities. For example, mathematical models developed from data across 11 clinical trials have demonstrated that optimizing drug administration timing—such as a 9.6-hour delay between pemetrexed-cisplatin and bevacizumab—can enhance therapeutic efficacy, with simulations indicating a 20.7% improvement in tumor reduction for a significant majority of patients. Furthermore, incorporating multimodal data from radiology, pathology, and genomics paves the way for more precise treatment decision-making, ultimately aiming to improve patient outcomes in NSCLC [28, 21, 36, 22, 40].

3.4 Recent Advancements and Clinical Trials

Recent advancements in neoadjuvant therapy for NSCLC have been driven by innovative research methodologies and clinical trials focused on addressing tumor heterogeneity and resistance mechanisms. The integration of deep learning models, such as the two-step multiple instance learning (MIL) approach, has improved treatment responder identification by incorporating attention mechanisms and weak labels, enhancing predictive tool precision [1]. Additionally, novel deep neural network (DNN) models have translated pharmacogenomic features from in vitro studies into predictive tools for drug responses in tumors, significantly improving prediction accuracy.

Advanced imaging techniques, including molecular MRI, have shown potential in detecting early biological changes associated with treatment response, thereby enhancing cancer immunotherapy management through timely and accurate assessments of therapeutic efficacy [41]. The use of QuanTAV features as predictive and prognostic biomarkers further highlights the role of advanced radiomics in correlating treatment responses and survival outcomes across various cancer types [42].

Clinical trials have focused on optimizing treatment timing and scheduling to enhance therapeutic efficacy. The CheckMate 067 immunotherapy trial has provided critical insights into immunotherapy's long-term effects, establishing it as a cornerstone of cancer treatment [19]. The combination of nivolumab with chemotherapy has demonstrated significantly improved event-free survival (EFS) and higher rates of pathologic complete response compared to chemotherapy alone, underscoring the potential of combination therapies to enhance patient outcomes [43]. Moreover, the Modestly-Weighted Log-Rank Test (MWLR) has improved the detection of treatment effects in trials with delayed responses, offering a robust alternative to traditional methods [44].

Exploration of novel therapeutic strategies, such as inhibiting JAK-STAT signaling, has emerged as a promising approach to enhance NSCLC treatment efficacy [21]. The development of targeted nanoconjugate platforms, like TBN, which co-deliver siRNA and gefitinib, has led to enhanced oncogene knockdown and sensitization of KRAS mutant NSCLC cells to TKI treatment, further expanding the therapeutic arsenal [45].

Mathematical modeling frameworks have also been instrumental in predicting treatment outcomes and exploring combination therapy dynamics, providing insights previously less addressed [4]. Future research should investigate Orai3's role in other cancer types, explore calcium signaling dynamics in various contexts, and evaluate potential pharmacological inhibitors of Orai3 to enhance treatment efficacy [27].

These advancements reflect the dynamic nature of research in neoadjuvant therapy for NSCLC, with ongoing efforts to integrate cutting-edge methodologies and clinical trial designs to refine therapeutic strategies and improve patient outcomes. The continued exploration of individualized treatment plans and emerging therapies is crucial for enhancing outcomes for stage III NSCLC patients, as evidenced by integrating mathematical modeling to optimize the synergy between radiotherapy and immunotherapy [3].

4 Chemotherapy Resistance

4.1 Biological Mechanisms of Chemotherapy Resistance

Chemotherapy resistance in non-small cell lung cancer (NSCLC) is driven by intrinsic and acquired mechanisms that compromise treatment efficacy. Intrinsic resistance involves genetic and epigenetic alterations that enhance tumor cell survival through increased drug efflux, enhanced DNA repair, and detoxification processes, notably affecting platinum-based drugs like cisplatin [16]. Acquired resistance emerges from adaptive changes under chemotherapy's selective pressure, promoting tumor survival and proliferation [34].

The tumor microenvironment plays a pivotal role in resistance, where the architecture of tumor vasculature can lead to uneven drug distribution, resulting in suboptimal concentrations in certain regions [42]. Imaging limitations, such as those of PET, further complicate accurate tumor targeting [41].

Molecular mechanisms also contribute significantly. Long non-coding RNAs like AFAP1-AS1 can suppress microRNAs such as miR-139-5p, activating pathways like RRM2/EGFR/AKT that enhance cancer cell survival and reduce chemotherapy efficacy [46]. Additionally, upregulation of PD-L1 in tumors inhibits anti-tumor immune responses, presenting a barrier to treatment [4].

These mechanisms complicate treatment outcome predictions. Traditional clinical trial designs often fail to account for the complexities of tumor biology, necessitating advanced methodologies [18]. Deep neural networks (DNNs) have shown promise in enhancing predictive power by optimizing feature resolution, improving response prediction accuracy [39]. Cross-Scale Sensitivity Analysis (CSSA) provides insights into molecular changes affecting cellular behavior, guiding strategies to combat resistance [8].

Advanced statistical methods, such as the studentized permutation method, offer robust tools for analyzing treatment effects, controlling type-I error rates, and ensuring valid confidence intervals under non-exchangeable data conditions [7]. These methodologies, along with reliable biomarkers, are essential for personalizing therapeutic interventions and improving patient outcomes in chemotherapy resistance contexts. Employing estimand and target trial frameworks enhances clarity in defining estimands and managing intercurrent events, ultimately improving the understanding of treatment effects [20].

Understanding the biological mechanisms underlying chemotherapy resistance in NSCLC is crucial for devising innovative strategies to overcome these challenges and enhance treatment efficacy. Integrating individual patient data can refine statistical inference, leading to more accurate estimates and robust conclusions in clinical trials [47]. Targeted nanoconjugate platforms that co-deliver siRNA and gefitinib present promising strategies for sensitizing resistant NSCLC cells to treatment [45].

4.2 Strategies to Overcome Chemotherapy Resistance

Addressing chemotherapy resistance in NSCLC requires a multifaceted approach, integrating molecular targeting, advanced imaging, and personalized treatment regimens. Exploiting metabolic vulnerabilities, such as targeting cystine uptake pathways, can enhance treatment efficacy. The role of Orai3 in calcium entry and AKT pathway activation is critical in chemoresistance, suggesting that targeting these pathways could offer new avenues for overcoming resistance [27].

Mathematical modeling and optimal control strategies provide frameworks for personalizing treatment regimens, enabling simulations of tumor-immune interactions and optimizing treatment schedules for improved outcomes [5]. These models are essential for understanding resistance dynamics and developing counteractive strategies. Learning-based sensitivity analysis methods are crucial for managing uncertainties in patient-specific parameters, vital for addressing chemotherapy resistance [48].

Advanced imaging techniques, like the QuanTAV approach, provide clinically relevant insights into tumor vasculature often overlooked by traditional methods [42]. This capability is crucial for enhancing chemotherapy precision by emphasizing tumor-related regions and potentially overcoming resistance. Additionally, developing predictive biomarkers for patient responses to combined therapies is critical, as understanding the long-term effects of vascular normalization could significantly improve therapeutic outcomes [14].

Challenges persist, including tumor heterogeneity and varying drug resistance dynamics among patients and tumor types [2]. Studies often lack long-term data, and the effectiveness of newer therapies in the adjuvant setting remains uncertain. Delays in immune response can lead to uncontrolled tumor growth despite treatment, underscoring the need for robust analytical frameworks to address these issues [17].

Future research should prioritize understanding NSCLC biology and developing effective early detection methods [6]. A comprehensive approach integrating targeted molecular interventions, advanced imaging, mathematical modeling, and personalized treatment strategies holds promise for overcoming chemotherapy resistance in NSCLC. Continued research is essential to refine these strategies and enhance therapeutic effectiveness in this challenging landscape.

4.3 Role of Immunotherapy in Addressing Resistance

Immunotherapy offers a promising strategy for overcoming chemotherapy resistance in NSCLC by leveraging the immune system to target resistant tumor cells. Incorporating immune checkpoint inhibitors (ICIs) into treatment regimens enhances efficacy by rejuvenating exhausted T cells and promoting sustained anti-tumor responses [49]. This strategy is particularly relevant given the challenges posed by intratumor heterogeneity (ITH), which fosters diverse tumor cell populations with varying susceptibilities [50].

The adaptive nature of tumor cell populations, characterized by cyclic dynamics in treatment responses, necessitates flexible and personalized therapeutic strategies that adapt to the evolving tumor landscape [51]. Immunotherapy may address these challenges by targeting specific metabolic pathways linked to oxidative stress resistance, such as cystine uptake, thereby enhancing existing therapies' effectiveness [35].

The tumor microenvironment significantly modulates immune responses and contributes to chemotherapy resistance. Understanding these interactions is crucial for optimizing immunotherapeutic interventions and developing reliable patient selection biomarkers [33]. Disruption of key signaling pathways, such as those mediated by Orai3 channels, which contribute to cisplatin resistance through calcium signaling, presents a viable target for enhancing immunotherapy efficacy in resistant NSCLC cases [27].

Research into the unfolded protein response (UPR) has highlighted how cancer cells adapt to therapeutic stress, revealing potential targets for overcoming drug resistance [17]. Integrating these insights with immunotherapeutic strategies could disrupt the adaptive mechanisms facilitating cancer cell survival under chemotherapeutic pressure.

Future research should emphasize personalized medicine approaches that incorporate individual genetic profiles, tumor microenvironment dynamics, and novel combination therapies that synergize with immunotherapy to combat resistance [34]. Vaccine therapy, particularly combined with surgery, offers additional avenues for enhancing immune responses and improving patient outcomes [52].

The complex role of immunotherapy in addressing chemotherapy resistance in NSCLC encompasses several key strategies: optimizing treatment protocols to enhance immune responses, specifically targeting resistance mechanisms exploited by tumors, and employing personalized therapeutic approaches that consider individual patient and tumor characteristics. Advances in biomaterials and drug delivery systems, such as nanoparticles and engineered T cells, aim to improve immunotherapy efficacy while minimizing adverse effects. The integration of immune checkpoint inhibitors, particularly those targeting PD-1 and PD-L1, has transformed treatment paradigms by providing durable responses in some patients, underscoring the need for ongoing research into predictive biomarkers and combination therapies to maximize therapeutic benefits [26, 24, 53, 54].

5 Impact on Surgical Decision-Making

5.1 The Role of Surgical Decision-Making

In managing NSCLC, surgical decision-making is pivotal, especially with neoadjuvant therapies like chemotherapy and immunotherapy that alter tumor characteristics and prognosis. Evaluating the tumor's response through pathologic assessment of residual viable tumor (RVT) in both the primary tumor and lymph nodes is essential, alongside assessing surgical resectability and prior therapy complications. This is crucial for patients with locally advanced NSCLC, where multimodal treatments significantly impact survival rates [52, 20, 43, 55, 11].

Radiomic feature analysis has become instrumental in refining surgical planning by providing predictive insights into tumor biology and treatment response, thereby guiding surgical interventions [38]. The use of immune checkpoint inhibitors (ICIs) in neoadjuvant settings further complicates surgical decisions due to variable efficacy among patients, necessitating predictive markers for optimal surgical planning [56].

5.2 Impact of Intra-Tumor Heterogeneity

ITH profoundly affects surgical decision-making and treatment outcomes in NSCLC. Variability in tumor characteristics, including diverse cancer cell sub-populations, complicates therapeutic response assessments and surgical resectability. Understanding ITH is crucial for optimizing treatment strategies, as it influences immune response efficacy and the integration of multimodal data for personalized therapy, ultimately impacting survival and quality of life [57, 28, 22, 50, 11]. Tumor microenvironment abnormalities, such as vasculature, mediate ITH by affecting immune cell infiltration [14].

Radiomic analysis effectively captures ITH complexity, offering insights into tumor behavior and treatment response. By analyzing imaging data, researchers can identify patterns correlating with genetic and phenotypic diversity within tumors, aiding in surgical strategy formulation. Advanced methodologies that extract extensive radiomic features enhance predictive modeling, improving precision medicine outcomes [38, 58, 23]. Addressing ITH challenges through multidisciplinary approaches is essential for effective NSCLC management, improving the likelihood of complete tumor resection and long-term survival.

5.3 Impact of Treatment Timing and Strategy

The timing and strategic planning of neoadjuvant therapy are critical for surgical outcomes in NSCLC. The administration schedule of therapies like chemotherapy and immunotherapy influences tumor reduction and resectability. Strategic sequencing can alter the tumor microenvironment and immune response, affecting neoadjuvant efficacy [14].

Optimal treatment timing requires precise coordination to maximize therapeutic effects while minimizing healthy tissue impact. For instance, using antiangiogenic agents to normalize tumor vasculature before chemotherapy or immunotherapy can enhance drug delivery and immune infiltration, improving outcomes [14]. Personalized treatment plans based on genetic and molecular profiles can tailor neoadjuvant therapies to target tumor vulnerabilities, enhancing pathological response likelihood.

Advanced imaging techniques, along with comprehensive molecular profiling, inform treatment decisions by revealing insights into tumor heterogeneity and potential resistance mechanisms. These methods integrate multimodal data, enabling predictive biomarker identification for therapy stratification. AI advancements are further enhancing complex dataset interpretation, advancing precision oncology [42, 38, 41, 23].

Mathematical modeling and computational simulations aid in predicting treatment outcomes and optimizing timing strategies, exploring various treatment scenarios to identify effective approaches for individual patients [36]. Leveraging these tools enhances neoadjuvant therapy precision and surgical decision-making, improving NSCLC patient outcomes.

6 Optimizing Patient Care

6.1 Personalized Treatment Plans

Personalized treatment plans in NSCLC are pivotal for enhancing therapeutic efficacy and patient outcomes by tailoring neoadjuvant therapies to individual tumor characteristics through integration of genetic, phenotypic, and clinical data. This individualized approach improves therapeutic precision and minimizes adverse effects by targeting specific tumor vulnerabilities. Advanced delivery technologies, such as nanoparticles and T cell-based systems, enhance immunotherapy outcomes while reducing side effects like autoimmunity and inflammation [53, 20]. Mathematical models simulating tumor-immune interactions are crucial for optimizing therapy timing and sequencing, utilizing optimal control theory to maximize patient outcomes [59, 36]. These models explore tumor composition and immune responses, guiding the selection of therapeutic agents and schedules tailored to individual patients.

The integration of multimodal data, including CT, PET, and genomic information, enriches personalized treatment plan development. Self-supervised learning frameworks extract embeddings from diverse sources, offering a comprehensive understanding of patient-specific factors influencing treatment outcomes and identifying crucial biomarkers and molecular targets [29]. Future research should focus on optimizing treatment formulations and exploring innovative therapeutic combinations, particularly through advanced biomaterials and drug delivery systems. Understanding tumor molecular features is essential for tailoring combinations, especially for targeted therapies in NSCLC, where integrating immunotherapy with existing modalities could significantly enhance patient outcomes [53, 20, 21, 30]. Promising avenues include targeted nanoconjugate platforms co-delivering siRNA and gefitinib to sensitize resistant NSCLC cells and combinatorial approaches targeting UPR pathways alongside conventional therapies to address resistance mechanisms within the tumor microenvironment.

6.2 Biomarkers and Molecular Profiling

Biomarkers and molecular profiling are vital for personalizing neoadjuvant therapy in NSCLC, offering insights into tumor-specific characteristics and responses that guide treatment decisions. Reliable biomarker identification and validation are essential for optimizing therapeutic strategies by predicting patient responses and tailoring interventions to distinct tumor profiles [16]. Radiomic features from imaging datasets provide a non-invasive means to assess tumor heterogeneity and predict therapeutic outcomes, informing personalized treatment plans [42]. Integrating molecular profiling with clinical data refines neoadjuvant therapy precision by identifying unique intervention targets,

facilitating tailored treatment regimens that address specific tumor vulnerabilities [21]. This approach is particularly beneficial in immunotherapy, where selecting appropriate biomarkers significantly impacts patient outcomes by identifying individuals most likely to benefit.

Advanced statistical methods and modeling frameworks are crucial for refining biomarker selection and validation. The ARMADA method, for instance, selects and ranks covariates in high-dimensional data while accounting for dependencies, essential for personalized treatment plans [48]. The RadioPathomics method enhances predictive performance by combining diverse classifiers through late fusion to reduce individual error rates [23]. Rigorous methodologies ensure selected biomarkers provide meaningful insights into tumor behavior and therapy response, enhancing neoadjuvant treatment personalization. Learning-based sensitivity analysis frameworks identify key parameters impacting treatment outcomes, visualized through dashboards, further aiding personalization [37].

6.3 Multidisciplinary Approaches

Optimizing NSCLC patient care and treatment outcomes requires a comprehensive multidisciplinary approach, integrating expertise from oncology, radiology, pathology, and computational modeling. Leveraging multimodal data, including clinical records, imaging, and genomics, enhances precision oncology practices and informs treatment decision-making through sophisticated machine-learning algorithms. Recent advancements, such as the DyAM model and multimodal late fusion techniques, demonstrate the potential of combining diverse data sources to predict responses to therapies like PD-(L)1 blockade and radiation treatment, leading to more personalized and effective patient management strategies [22, 23]. This integrated framework is essential for addressing NSCLC complexities, particularly in neoadjuvant therapy, where treatment modalities and tumor biology interplay requires specialist coordination.

Incorporating advanced modeling techniques, such as multi-scale models encompassing cellular and molecular dynamics, is crucial for enhancing treatment strategy precision [24]. These models provide insights into optimal therapy timing and sequencing, allowing personalized treatment plans that maximize therapeutic efficacy while minimizing adverse effects [36]. Developing larger, publicly accessible datasets and exploring new deep learning architectures are pivotal for improving radiogenomic model robustness and clinical applicability, supporting the multidisciplinary approach to patient care [10]. Advancements in targeted therapies and immunotherapy have significantly improved NSCLC patient survival rates and quality of life, underscoring the importance of ongoing research and cross-disciplinary collaboration [9]. Incorporating emerging biomarkers and novel agents into treatment regimens is crucial for overcoming resistance and enhancing existing therapy effectiveness [21]. Managing high-dimensional data with correlated covariates, as demonstrated by methodologies like ARMADA, highlights the need for multidisciplinary strategies that optimize patient care through improved selection accuracy and treatment personalization [48].

Future research should refine models with clinical data, explore additional regulatory mechanisms, and test predictions in diverse cancer types to enhance the multidisciplinary approach to NSCLC treatment [49]. Collaboration among researchers and clinicians from various fields ensures patient care is optimized through integrating cutting-edge technologies and innovative therapeutic strategies.

7 Conclusion

This survey has provided a comprehensive examination of neoadjuvant therapy in the context of non-small cell lung cancer (NSCLC), underscoring the pivotal roles of chemotherapy and immunotherapy in enhancing treatment outcomes and surgical success. The complexity of managing NSCLC is underscored by persistent challenges such as tumor heterogeneity and chemotherapy resistance, necessitating sophisticated modeling and personalized treatment strategies to improve therapeutic outcomes and patient prognoses.

Future research directions should focus on exploring innovative therapeutic combinations, particularly integrating antiangiogenic therapies with immunotherapies to target the metabolic vulnerabilities inherent in NSCLC. The advancement of predictive biomarkers and the adoption of novel trial designs employing surrogate endpoints are crucial for accelerating the development of effective treatments for early-stage NSCLC. Additionally, the synergy of machine learning and sensitivity analysis offers a promising avenue for optimizing drug delivery systems.

The continual evolution of neoadjuvant therapy practices relies heavily on innovation and cross-disciplinary collaboration to improve patient outcomes in NSCLC. Future studies should incorporate advanced modeling frameworks, such as three-dimensional simulations and the integration of diverse biological pathways, to enhance predictive accuracy. Moreover, extensive clinical studies are imperative for validating emerging molecular MRI techniques, leveraging AI to enhance imaging precision, and developing comprehensive multimodal imaging strategies. Expanding datasets and incorporating T-cell behavior parameters will further refine and personalize treatment approaches in NSCLC.

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