A Survey of Multiple Primary Lung Cancers Treatment Advances and Precision Medicine Approaches

www.surveyx.cn

Abstract

Multiple primary lung cancers (MPLCs) present unique diagnostic and therapeutic challenges due to their independent origin and diverse histological and genetic profiles. This survey paper provides a comprehensive examination of modern oncology approaches to MPLC treatment, emphasizing surgical resection strategies, targeted therapy, immunotherapy, precision medicine, and molecular diagnostics. Advanced surgical techniques, including image-guided surgery, have significantly enhanced the precision of tumor resections, particularly in complex cases involving MPLCs. The development of targeted therapies, such as EGFR tyrosine kinase inhibitors (TKIs), has revolutionized the treatment of non-small cell lung cancer (NSCLC) by targeting specific molecular pathways and genetic mutations. However, the emergence of resistance mechanisms, such as secondary mutations and alternative signaling pathways, poses significant challenges to treatment efficacy. Immunotherapy, particularly immune checkpoint inhibitors targeting PD-1 and PD-L1, has also shown promise in improving patient outcomes by reactivating the immune system to target cancer cells. Combination strategies integrating immunotherapy with targeted therapies and other modalities offer a promising approach to overcoming resistance mechanisms and optimizing treatment outcomes. The integration of precision medicine and molecular diagnostics, including liquid biopsy techniques, machine learning, and artificial intelligence, has further enhanced the precision and personalization of MPLC treatment. However, challenges related to tumor heterogeneity, data integration, and privacy concerns remain significant barriers to the effective implementation of precision medicine in MPLC management. Future research should focus on addressing these challenges, refining methodologies, and exploring novel therapeutic targets to fully realize the potential of precision medicine in transforming the landscape of lung cancer treatment. This comprehensive survey provides valuable insights for clinicians and researchers, highlighting the importance of integrating various treatment strategies to address the complexities and heterogeneity of MPLCs and improve patient outcomes.

1 Introduction

1.1 Overview of Multiple Primary Lung Cancers

Multiple primary lung cancers (MPLCs) involve the presence of multiple distinct lung cancers in a patient, each arising independently within lung tissue [1]. This condition presents diagnostic and therapeutic challenges, as each tumor may differ in histological type, genetic mutations, and biological behavior. MPLCs significantly contribute to the global lung cancer burden, which is the most prevalent cancer and a leading cause of cancer-related mortality [2]. Survivors of an initial primary lung cancer (IPLC) face a heightened risk of developing a second primary lung cancer

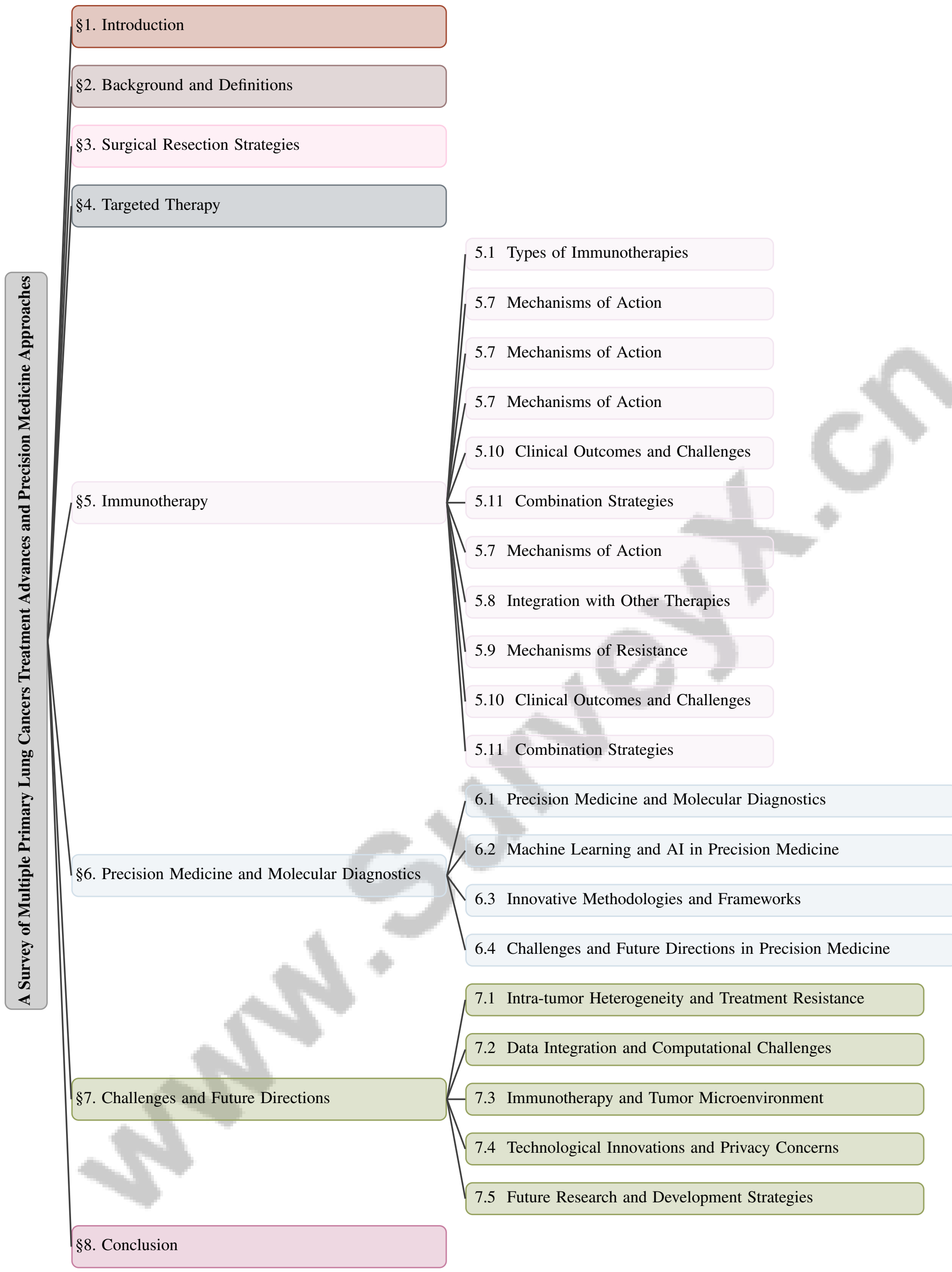

Figure 1: chapter structure

(SPLC), with studies indicating a 10-year risk that necessitates vigilant monitoring and tailored treatment strategies [3].

The complexity of MPLCs is compounded by the heterogeneity of lung cancer subtypes. For example, small-cell lung cancer (SCLC) and non-small cell lung carcinoma (NSCLC) exhibit significant differences in biology and clinical management. Understanding the molecular pathways driving tumor progression in lung adenocarcinoma (ADC), a subtype of NSCLC, is essential for developing targeted therapies [4]. Advances in molecular diagnostics, including liquid biopsy techniques, have improved early detection and personalized treatment of lung cancers, offering significant promise in managing MPLCs [5]. Addressing the challenges posed by MPLCs remains a critical area of research and clinical focus [6].

1.2 Importance of Advanced Treatment Strategies

Advanced treatment strategies are essential for managing multiple primary lung cancers (MPLCs) due to their inherent complexity and heterogeneity. Traditional therapeutic approaches often fall short, particularly in addressing the diverse biological behaviors and genetic profiles of MPLCs [7]. The complexity of medical imaging and the need for rapid, accurate interpretation in clinical decision-making highlight the importance of advanced strategies [8]. Moreover, the immunosuppressive tumor microenvironment, characterized by abnormal vasculature, limits the effectiveness of current immunotherapies, necessitating innovative strategies to overcome these barriers [9].

Precision oncology is crucial for tailoring individualized treatment strategies, leveraging patient heterogeneity to enhance clinical outcomes [10]. This approach customizes therapeutic interventions based on the unique molecular and genetic characteristics of each tumor, optimizing treatment efficacy and minimizing adverse effects [11]. The emergence of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in patients with EGFR-mutant NSCLC further underscores the need for adaptive strategies that respond to evolving tumor dynamics [7].

Recent advancements in predictive modeling and data integration have facilitated personalized treatment strategies, improving patient outcomes [12]. A significant challenge lies in identifying the most relevant clustering structures for specific tasks, particularly in disease subtyping, where different clusters may correspond to varying prognoses or treatment responses [13]. Transitioning from traditional reactive healthcare to a proactive approach that emphasizes disease prevention and early detection is vital in addressing MPLC challenges [14]. This proactive stance is supported by the development of effective combination therapies that can overcome drug resistance and enhance therapeutic efficacy [15].

Managing MPLCs is further complicated by the need to address multiple prioritized outcomes in clinical interventions, necessitating a comprehensive approach that integrates various treatment modalities [16]. Improved methodologies in cancer detection, diagnosis, and treatment outcomes are essential for optimizing resource allocation and enhancing operational efficiency in large-scale healthcare networks. Collectively, these advanced strategies are integral to addressing the multifaceted nature of MPLCs, ultimately contributing to improved clinical outcomes and patient survival.

1.3 Integration of Modern Oncology Approaches

Integrating modern oncology approaches into treatment plans for multiple primary lung cancers (MPLCs) is a dynamic process aimed at improving patient outcomes through advancements in precision medicine, targeted therapy, and immunotherapy. Developing comprehensive datasets for identifying and diagnosing lung nodules is crucial for advancing computer-aided diagnosis (CAD) methods, enhancing precision medicine initiatives [1]. These datasets enable the creation of robust algorithms that accurately interpret complex medical images, essential for tailoring individualized treatment strategies.

Targeted therapies have significantly evolved, with research categorizing methodologies into frameworks that highlight the progression of lung cancer treatments through molecular targeting [11]. Such frameworks allow clinicians to identify specific molecular pathways and genetic mutations for therapeutic exploitation, customizing treatment plans to the unique molecular profiles of tumors. This approach is particularly relevant in MPLCs, where tumor heterogeneity necessitates precise interventions.

The integration of antiangiogenic therapies with cancer immunotherapy represents another frontier in modern oncology, aimed at enhancing therapeutic efficacy and overcoming immune evasion by tumors [9]. By addressing the abnormal vasculature and immunosuppressive microenvironment characteristic of many lung cancers, these combined strategies hold promise for improving clinical outcomes in MPLC patients.

Moreover, applying novel adaptive algorithms that leverage real-time data is pivotal in optimizing resource distribution across healthcare networks, enhancing operational efficiency and ensuring timely, appropriate patient care [17]. Such innovations are integral to successfully implementing modern oncology approaches, facilitating the seamless integration of advanced therapeutic modalities into clinical practice.

Insights from regenerative processes in normal tissue repair have also shed light on how cancer cells may co-opt these mechanisms during tumor progression, suggesting potential therapeutic targets to disrupt tumor growth [18]. Understanding these processes enriches the strategies available to oncologists in managing MPLCs, underscoring the importance of a multidisciplinary approach in modern cancer care.

1.4 Structure of the Survey

This survey is organized into several comprehensive sections to thoroughly examine the current landscape and advancements in treating multiple primary lung cancers (MPLCs). The paper begins with an *Introduction* that establishes the foundation for understanding MPLCs, emphasizing the significance of advanced treatment strategies and integrating modern oncology approaches. This is followed by a detailed *Background and Definitions* section, which delineates the distinctions of MPLCs from other lung cancers and elucidates key concepts such as targeted therapy, immunotherapy, precision medicine, and molecular diagnostics.

The survey then explores *Surgical Resection Strategies*, discussing the latest advancements in surgical techniques and their integration with other therapies, including image-guided surgery, comparisons between segmentectomy and lobectomy, and frameworks for evaluating surgical effectiveness. The focus subsequently shifts to *Targeted Therapy*, highlighting the development and application of targeted therapies, specific molecular pathways, drug classes, and mechanisms of resistance.

The following section delves into the multifaceted role of immunotherapy in cancer treatment, exploring various types—including immune checkpoint inhibitors and adoptive cell therapies—alongside their mechanisms of action, clinical outcomes, and innovative combination strategies aimed at enhancing treatment efficacy while mitigating adverse effects. This analysis also addresses challenges of resistance to single-agent therapies and highlights advancements in delivery technologies and combination therapies that optimize patient responses and improve overall therapeutic effectiveness [9, 19, 20, 21, 22]. Following this, the survey discusses *Precision Medicine and Molecular Diagnostics*, emphasizing the importance of molecular diagnostics, machine learning and AI applications, innovative methodologies, and future directions in precision medicine.

The penultimate section, *Challenges and Future Directions*, identifies current challenges in MPLC treatment, such as intra-tumor heterogeneity and data integration issues, and discusses potential future research and development strategies. The survey concludes with a *Conclusion*, summarizing key points discussed and reinforcing the importance of integrating various treatment strategies to improve patient outcomes. This structured approach ensures a comprehensive understanding of the complexities and advancements in managing MPLCs, providing valuable insights for clinicians and researchers in the field.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Definitions and Distinctions of Multiple Primary Lung Cancers

Multiple primary lung cancers (MPLCs) are defined by the presence of multiple independent tumors within the lungs, each exhibiting unique histopathological characteristics [1]. This distinguishes MPLCs from metastatic lung cancer, where secondary tumors originate from a primary tumor. Accurate subclassification of non-small-cell lung cancer (NSCLC) is critical for distinguishing MPLCs, thereby enhancing diagnostic precision and the effectiveness of targeted therapies and immunotherapy [23]. Survivors of an initial primary lung cancer (IPLC) are at a heightened risk of a second primary lung cancer (SPLC), particularly after five years, necessitating vigilant monitoring and personalized treatment plans to address the distinct biological behaviors and genetic mutations of each tumor [3, 2]. The complexity of MPLCs demands individualized treatments to manage tumor heterogeneity and accurately assess treatment responses, distinguishing between true progression and pseudo-progression, especially in immunotherapy [24]. The regenerative and stem-like properties of metastatic lung cancer cells further complicate immune surveillance [18]. Liquid biopsy offers a non-invasive alternative to traditional biopsies, enabling real-time monitoring of genetic mutations and tumor dynamics, which is crucial for managing the heterogeneity of MPLCs [5]. Integrating advanced diagnostics and personalized therapies is essential for overcoming the challenges posed by MPLCs and improving patient outcomes [6].

2.2 Key Concepts in Cancer Treatment

Lung cancer treatment is grounded in key concepts that enhance diagnostic precision and therapeutic efficacy. Targeted therapies have revolutionized NSCLC management by focusing on specific molecular pathways and genetic alterations, leading to therapies tailored to each tumor's molecular characteristics, often surpassing traditional chemotherapy [25]. The heterogeneity of lung cancer necessitates advanced diagnostic and therapeutic strategies, with the identification of relevant clustering structures within high-dimensional omics data being crucial for stratified medicine and personalized treatment plans [13]. Precision medicine, a cornerstone of modern oncology, customizes healthcare based on genetic, environmental, and lifestyle factors to optimize treatment strategies and clinical outcomes. This approach uses biomarkers to personalize interventions, predict treatment responses, and inform therapeutic decisions, with technologies like next-generation sequencing and machine learning enhancing patient-therapy matching [26, 27, 28, 29, 30]. Combination cancer therapies (CCTs) integrate various modalities, such as chemoimmunotherapy and chemoradiotherapy, to overcome resistance and improve efficacy [25]. AI technologies in cancer treatment enhance diagnostic accuracy and therapeutic precision by analyzing complex medical data to identify novel targets and optimize regimens, demonstrating the transformative potential of AI in oncology [31, 12, 32, 33, 30]. The integration of targeted therapies, immunotherapies, and advancements in genomic medicine provides a robust framework for developing sophisticated lung cancer treatment strategies, particularly for NSCLC, by tailoring approaches based on individual tumor molecular characteristics and leveraging ongoing clinical trials [25, 26, 34]. This underscores the importance of personalized approaches and innovative methodologies in improving patient outcomes and advancing oncology.

3 Surgical Resection Strategies

A thorough grasp of surgical resection strategies is pivotal for advancing patient outcomes in lung cancer treatment. This section delves into notable advancements in image-guided surgery, a transformative development enhancing surgical precision. Utilizing cutting-edge imaging technologies, this approach improves tumor localization and aids in preserving surrounding healthy tissue, setting the stage for evaluating its impact on surgical efficacy and patient prognosis in lung cancer management. Table 2 offers a detailed comparison of key features in image-guided surgery, segmentectomy versus lobectomy, and frameworks for surgical effectiveness, illustrating their respective contributions to enhancing surgical precision and patient care in lung cancer treatment. As illustrated in Figure 2, the hierarchical structure of surgical resection strategies in lung cancer treatment underscores the significance of these advancements. The figure highlights key developments in image-guided surgery, compares segmentectomy with lobectomy, and provides a framework for assessing surgical effectiveness. Furthermore, it integrates surgical strategies with other therapeutic modalities, emphasizing technological enhancements, precision medicine, and data-driven insights that collectively aim to optimize patient outcomes.

3.1 Advances in Image-Guided Surgery

Image-guided surgery has significantly enhanced the precision of lung cancer interventions by utilizing advanced imaging technologies for real-time visualization and accurate tumor delineation. The incorporation of photoacoustic imaging (PAI) exemplifies this progress, combining optical and ultrasound imaging to produce high-resolution images that distinguish healthy from cancerous tissues, thereby improving diagnostic and therapeutic outcomes [35]. Emphasizing real-time tumor delineation, these technologies increase surgical accuracy while reducing the risk of damaging adjacent healthy tissues, crucial in managing MPLCs characterized by tumor heterogeneity. Additionally, integrating image-guided surgery with data processing frameworks enhances precision medicine approaches by efficiently managing complex datasets generated during surgeries, enabling informed clinical decisions that optimize patient outcomes [36].

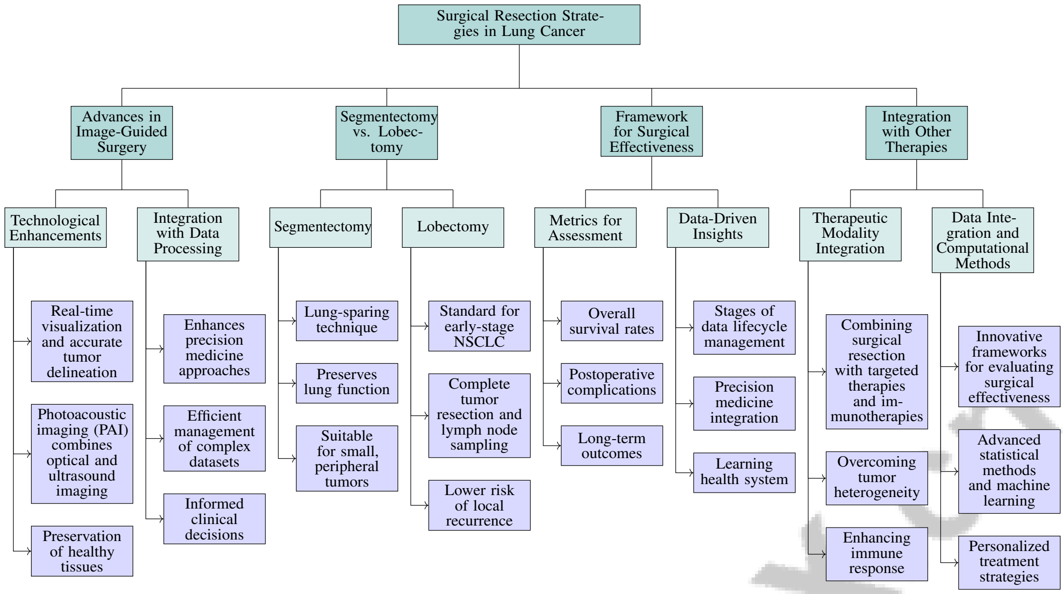

Figure 2: This figure illustrates the hierarchical structure of surgical resection strategies in lung cancer treatment, highlighting key advancements in image-guided surgery, the comparative analysis of segmentectomy versus lobectomy, a framework for assessing surgical effectiveness, and the integration of surgical strategies with other therapies. The diagram emphasizes technological enhancements, precision medicine, and data-driven insights to optimize patient outcomes.

3.2 Segmentectomy vs. Lobectomy

In early-stage NSCLC management, the choice between segmentectomy and lobectomy significantly impacts patient outcomes. Segmentectomy, a lung-sparing technique, involves resecting a specific lung segment, while lobectomy entails removing an entire lung lobe. Factors such as tumor size, location, and patient comorbidities influence this decision. Studies indicate that segmentectomy can preserve lung function and achieve oncological outcomes comparable to lobectomy for small, peripheral tumors [37]. It is particularly beneficial for patients with compromised pulmonary reserve or high surgical risk, as it reduces postoperative morbidity and mortality. Conversely, lobectomy remains the standard for many early-stage NSCLC cases, especially where complete tumor resection and adequate lymph node sampling are critical, offering a lower risk of local recurrence for larger or centrally located tumors.

The comparative benefits of these two surgical approaches are illustrated in Figure 3, which highlights their respective advantages and the role of ongoing research and technological advancements in surgical techniques. The decision must be individualized, considering tumor characteristics and the patient's overall health. Ongoing research and clinical trials are essential to refine surgical techniques and improve patient outcomes, particularly as lung cancer treatment evolves with advancements in immunotherapy and targeted therapies [25, 38, 37]. The integration of advanced imaging technologies and minimally invasive techniques further enhances the precision and safety of both segmentectomy and lobectomy.

3.3 Framework for Surgical Effectiveness

Assessing the effectiveness of surgical interventions in lung cancer treatment necessitates a comprehensive framework that includes metrics such as overall survival rates, postoperative complications, and long-term outcomes. Table 1 provides a comprehensive overview of representative benchmarks pertinent to assessing the effectiveness of surgical interventions in lung cancer treatment, highlighting their role in facilitating precision medicine through structured data management. This framework is particularly relevant in comparing segmentectomy and lobectomy, two common surgical options for early-stage NSCLC. Studies suggest that segmentectomy can achieve survival outcomes comparable to lobectomy, especially for small, peripheral tumors, while preserving lung function and

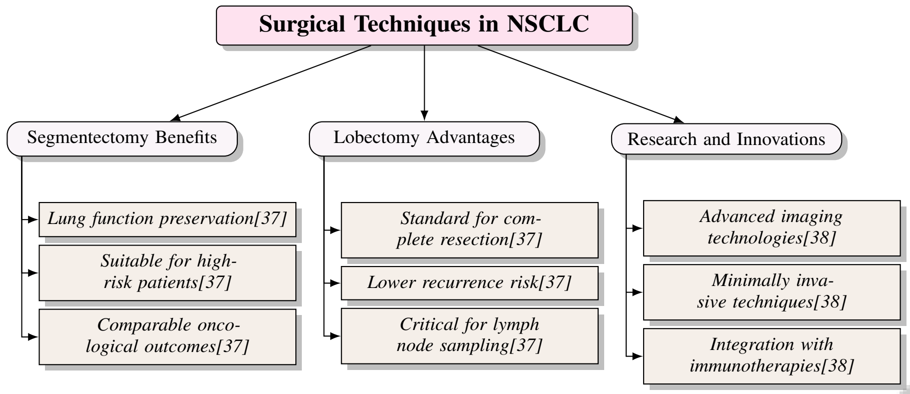

Figure 3: This figure illustrates the comparative benefits of segmentectomy and lobectomy in NSCLC management, highlighting their respective advantages and the role of ongoing research and technological advancements in surgical techniques.

Benchmark	Size	Domain	Task Format	Metric
CSTLND[1]	328	Lung Cancer Detection	Nodule Detection	ACC, QWK
Pulmonary-RadPath[2]	5,134	Pulmonary Pathology	Hierarchical Classification	mAUC
PMV[39]	4,567,208	Precision Medicine	Data Integration	Concept Coverage

Table 1: This table presents a selection of representative benchmarks utilized in the evaluation of surgical effectiveness within the context of lung cancer treatment. It details the benchmark names, their respective sizes, domains of application, task formats, and the metrics used to assess their performance.

reducing postoperative morbidity [37]. A structured approach incorporating stages of data lifecycle management—data ingestion, storage, processing, and querying—enables efficient organization and analysis of data, facilitating informed clinical decisions that optimize surgical strategies [36]. This framework clarifies the comparative advantages and disadvantages of various surgical techniques and promotes precision medicine integration into surgical decision-making. By employing a retrieval system that identifies effective treatments based on individual patient factors, healthcare providers can align decisions with precision medicine principles, fostering a learning health system that optimizes clinical care and improves patient outcomes through data-driven insights [26, 40].

3.4 Integration with Other Therapies

Integrating surgical resection strategies with other therapeutic modalities is crucial in managing MPLCs, enhancing treatment efficacy and patient outcomes by leveraging various therapeutic strategies. Advances in image-guided surgery, such as PAI, provide real-time, high-resolution images that assist surgeons in accurately targeting cancerous tissues while preserving healthy structures [35]. This is vital for complex procedures like segmentectomy and lobectomy, especially in patients with compromised pulmonary function or multiple tumor sites [8]. Combining surgical resection with targeted therapies and immunotherapies effectively addresses the heterogeneity of MPLCs, often exhibiting diverse genetic mutations and resistance mechanisms [4]. This integration is essential for overcoming challenges posed by the immunosuppressive tumor microenvironment, which can impede traditional treatments [9]. Notably, combining antiangiogenic therapies with immunotherapy shows promise in normalizing tumor vasculature and enhancing immune response, improving therapeutic outcomes. Advances in data integration and computational methods have led to innovative frameworks for evaluating surgical effectiveness, empowering clinicians to analyze intricate datasets generated during procedures, extracting insights regarding the comparative advantages and potential risks of various surgical techniques. By integrating diverse data sources—including molecular, clinical, and imaging information—these frameworks enhance understanding of disease mechanisms and support personalized treatment strategies. Advanced statistical methods and machine learning algorithms interpret complex data, aiding in establishing evidence-based practices in precision medicine [36, 41, 42, 26]. Leveraging these tools enables healthcare professionals to make more informed decisions, enhancing the precision and effectiveness of surgical interventions for MPLCs.

Feature	Advances in Image-Guided Surgery	Segmentectomy vs. Lobectomy	Framework for Surgical Effectiveness
Precision Enhancement	Real-time Visualization	Lung-sparing Technique	Data-driven Insights
Patient Suitability	Mplcs Management	Compromised Pulmonary Reserve	Nsclc Early-stage
Integration Capability	Data Processing Frameworks	Minimally Invasive Techniques	Precision Medicine Integration

Table 2: The table provides a comparative analysis of three pivotal aspects in lung cancer surgical strategies: advances in image-guided surgery, segmentectomy versus lobectomy, and a framework for surgical effectiveness. Each category is evaluated based on precision enhancement, patient suitability, and integration capability, highlighting the technological and methodological advancements that contribute to optimizing patient outcomes.

4 Targeted Therapy

In recent years, the landscape of cancer treatment has evolved significantly, particularly with the advent of targeted therapies that focus on specific molecular alterations driving tumorigenesis. This shift towards precision oncology is especially evident in the treatment of multiple primary lung cancers (MPLCs), where understanding the underlying molecular mechanisms has become paramount. The subsequent subsection will delve into the intricate molecular pathways and targets that have emerged as focal points for therapeutic intervention, highlighting their relevance in enhancing treatment efficacy and personalizing patient care.

4.1 Molecular Pathways and Targets

The treatment of multiple primary lung cancers (MPLCs) has been significantly advanced through the development and application of targeted therapies, which focus on specific molecular pathways and genetic alterations within tumors. These targeted therapies represent a significant advancement in cancer treatment by providing a personalized approach that focuses on the unique molecular characteristics of each patient's tumor. Specifically designed to disrupt the activity of key molecules involved in cancer cell growth, progression, and metastasis, these therapies aim to selectively target dysregulated pathways, such as those influenced by alterations in tumor suppressor genes and oncogenes. This precision not only enhances the efficacy of treatment but also significantly reduces collateral damage to normal, healthy cells, addressing the limitations of traditional chemotherapy, which often affects both cancerous and non-cancerous cells indiscriminately. The integration of advanced molecular profiling and genomic analysis facilitates the identification of specific genetic alterations in tumors, paving the way for tailored therapeutic strategies that can improve patient outcomes and minimize the risk of treatment resistance and recurrence. [43, 44, 45, 46]

One of the primary molecular pathways targeted in lung cancer treatment is the epidermal growth factor receptor (EGFR) pathway. Mutations in the EGFR gene are prevalent in non-small cell lung cancer (NSCLC), particularly in adenocarcinoma, and are associated with tumor proliferation and survival [4]. Targeted therapies, such as EGFR tyrosine kinase inhibitors (TKIs), have been developed to specifically inhibit the activity of the mutated EGFR, leading to significant improvements in progression-free survival and quality of life for patients with EGFR-mutant NSCLC [7].

The PI3K/AKT/mTOR signaling pathway is a pivotal target in precision oncology, as it plays a crucial role in regulating cellular processes such as growth, metabolism, and survival. Dysregulation of this pathway is commonly observed in various cancers, contributing to tumor initiation and progression. Recent advancements in molecular profiling and targeted therapies have enabled the development of treatments that specifically address the genetic alterations within this pathway, highlighting the importance of personalized approaches in cancer therapy to improve patient outcomes and overcome challenges such as drug resistance. [43, 26, 45, 40, 47]. Dysregulation of this pathway is common in various cancers, including lung cancer, and is associated with tumor growth and resistance to conventional therapies . Targeting the PI3K/AKT/mTOR pathway with specific inhibitors has shown promise in overcoming resistance mechanisms and enhancing the efficacy of existing treatments.

Furthermore, the RAS-MAPK pathway, which plays a pivotal role in cell proliferation and survival, represents another significant target in the treatment of MPLCs. While direct inhibition of RAS has been challenging, recent advancements have led to the development of novel direct inhibitors that show potential in preclinical and clinical studies [35]. The importance of targeting RAS activation pathways is also emphasized, as these pathways contribute to the oncogenic process in lung cancer .

The JAK-STAT pathway is another critical target in the treatment of MPLCs, as it is involved in the regulation of immune responses and tumor progression. Inhibition of this pathway has shown potential in enhancing the effectiveness of immunotherapies and improving patient outcomes [25]. The integration of targeted therapies with other treatment modalities, such as immunotherapy and surgical resection, is crucial for addressing the complex biological landscape of MPLCs and achieving better clinical outcomes [4].

The ongoing research into molecular pathways and targets continues to expand the arsenal of targeted therapies available for MPLC treatment. "This progress is crucial for advancing precision oncology, as it facilitates the creation of more effective and personalized treatment strategies that take into account the distinct genetic and molecular characteristics of each tumor. By leveraging next-generation sequencing (NGS) technology, which allows for rapid and comprehensive analysis of genomic data, clinicians can identify specific genetic alterations driving tumor growth. This enables the development of sequencing-matched therapies, tailored to the unique molecular profile of individual tumors, ultimately aiming to enhance patient outcomes and address the inherent heterogeneity of cancer responses to treatment." [28, 45]. By leveraging these advances, clinicians can offer more tailored and effective treatments, ultimately improving patient survival and quality of life.

4.2 Drug Classes and Specific Inhibitors

Targeted therapy represents a paradigm shift in the treatment of multiple primary lung cancers (MPLCs), as it focuses on the specific molecular alterations driving tumor growth and progression. This innovative approach has facilitated the creation of diverse classes of targeted therapeutics and specific inhibitors that are meticulously designed to effectively engage and modulate dysregulated molecular pathways associated with cancer, enhancing the precision of treatment options tailored to individual patients' unique tumor profiles. [43, 45]

One of the most well-known classes of targeted therapies is the tyrosine kinase inhibitors (TKIs), which include drugs such as erlotinib, gefitinib, and afatinib. These inhibitors specifically target the epidermal growth factor receptor (EGFR) mutations, which are prevalent in a subset of non-small cell lung cancer (NSCLC) patients [4]. EGFR mutations are known to drive tumor growth and proliferation, making them critical targets for therapeutic intervention. The success of EGFR TKIs in improving progression-free survival and overall response rates has underscored the potential of precision medicine in the management of MPLCs [7].

In addition to EGFR inhibitors, other targeted therapies have been developed to address different molecular pathways implicated in MPLCs. Inhibitors targeting the PI3K/AKT/mTOR pathway have shown promise in overcoming resistance mechanisms and enhancing the efficacy of existing treatments . Inhibitors targeting the RAS-MAPK and JAK-STAT pathways have shown promising results in both preclinical and clinical studies, indicating their potential to enhance treatment options for patients with malignant pleural lung cancer (MPLC). Notably, recent advancements in allele-specific covalent inhibitors, particularly those aimed at the frequently mutated KRAS G12C in non-small-cell lung cancer, have opened new avenues for effectively targeting RAS-driven oncogenesis. Furthermore, the integration of these inhibitors with other therapeutic strategies, such as immune checkpoint inhibitors and combination therapies, could significantly improve patient outcomes by addressing the complex and heterogeneous nature of cancer. This evolving landscape underscores the importance of precision oncology, which tailors treatment based on individual genomic profiles and the specific molecular alterations present in tumors, thereby optimizing therapeutic efficacy for MPLC patients. [48, 45, 15, 49, 47]

The development and approval of targeted therapies for molecularly profiled lung cancers (MPLCs) signify a transformative leap in cancer treatment, as these therapies are specifically designed to address the unique genetic alterations present in individual patients' tumors. This advancement not only enhances treatment efficacy but also offers renewed hope for patients who previously faced limited options due to the complexities of their disease, underscoring the importance of precision medicine in tailoring interventions to the molecular characteristics of each patient's cancer. [43, 50, 26, 45, 46]. As our understanding of the molecular drivers of lung cancer continues to evolve, the identification and validation of novel therapeutic targets will be crucial in the ongoing effort to improve patient outcomes and extend survival in this challenging disease.

4.3 Drug Classes and Specific Inhibitors

In the context of multiple primary lung cancers (MPLCs), targeted therapy has emerged as a crucial innovation in cancer treatment, specifically designed to address the unique molecular alterations that drive tumor growth and progression. This approach not only enhances the precision of treatment by tailoring interventions to the genetic characteristics of individual tumors, but also marks a significant departure from traditional chemotherapy, offering the potential for improved patient outcomes and quality of life. Recent advancements in genomic medicine and drug development have further facilitated the identification of actionable genetic lesions, enabling oncologists to optimize therapeutic strategies through the integration of targeted therapies, immunotherapies, and chemotherapy. [43, 25]. The development of various drug classes and specific inhibitors has significantly improved treatment efficacy and patient outcomes. Among these, tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have emerged as a cornerstone in the management of non-small-cell lung cancer (NSCLC) . Notable examples include erlotinib, gefitinib, and osimertinib, which have demonstrated substantial progression-free survival benefits compared to traditional chemotherapy .

Osimertinib, a third-generation EGFR TKI, specifically targets the T790M resistance mutation, offering improved efficacy over first-generation inhibitors in patients with EGFR-mutant NSCLC . This targeted approach illustrates the transformative potential of precision medicine in improving cancer treatment outcomes by customizing therapies based on the unique molecular profile of individual tumors. By leveraging advancements in genomic analysis and molecular profiling, precision oncology seeks to address the inherent heterogeneity of tumors, which often leads to varied patient responses to standard treatments. This individualized strategy not only enhances the efficacy of therapies but also minimizes adverse effects by focusing on the specific genetic alterations driving cancer progression in each patient. Consequently, ongoing genomic studies are crucial for identifying the determinants of cancer development and tailoring treatment plans that optimize patient care and therapeutic effectiveness. [43, 26, 45, 27, 29]

In addition to EGFR inhibitors, the PI3K/AKT/mTOR signaling pathway has emerged as a critical target for precision oncology. This pathway plays a pivotal role in cell growth, survival, and proliferation, making it a prime candidate for therapeutic intervention [25]. Inhibitors targeting components of this pathway, such as PI3K, AKT, and mTOR, have been developed and are being evaluated in clinical trials for their potential to improve outcomes in patients with multiple primary lung cancers (MPLCs).

The RAS signaling pathway is another significant target in lung cancer treatment. Despite the historical challenges associated with directly targeting RAS proteins, recent advancements have led to the development of novel inhibitors that disrupt RAS-effector interactions and RAS processing pathways [35]. These innovative therapies hold promise for overcoming resistance mechanisms and improving clinical outcomes in patients with RAS-driven MPLCs.

The exploration of drug classes and specific inhibitors is an ongoing area of research in the field of oncology. As our understanding of molecular pathways and genetic mutations continues to evolve, the development of targeted therapies will play an increasingly crucial role in the personalized treatment of multiple primary lung cancers. This approach not only enhances the therapeutic efficacy of cancer treatments by tailoring interventions to the individual patient's genetic profile and disease characteristics but also significantly reduces adverse effects associated with therapies, such as autoimmunity and nonspecific inflammation. By leveraging advanced drug delivery technologies and precision medicine strategies, this method ultimately leads to improved patient quality of life and better survival outcomes. [6, 26, 16, 29, 21]

4.4 Mechanisms of Resistance

In the treatment of multiple primary lung cancers (MPLCs), the emergence of resistance to targeted therapies presents a significant challenge, often leading to treatment failure and disease progression. The development of resistance mechanisms can occur through various biological processes, which ultimately compromise the efficacy of targeted therapeutic interventions . A central issue in the treatment of MPLCs is the development of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), which are a mainstay in the management of non-small-cell lung cancer (NSCLC) with EGFR mutations [7].

One of the most well-documented resistance mechanisms is the acquisition of secondary mutations, such as the T790M mutation in the EGFR gene. This mutation alters the conformation of the EGFR protein, reducing the binding affinity of first-generation TKIs and leading to therapeutic resistance [7]. The emergence of such mutations necessitates the development of next-generation inhibitors that can effectively target these resistant variants, thereby extending the efficacy of targeted therapies.

Another challenge in the development of effective targeted therapies for MPLCs is the inherent heterogeneity of lung cancer. This heterogeneity is often reflected in the presence of multiple relevant clustering structures within high-dimensional omics datasets, complicating the identification of optimal therapeutic targets and strategies [13]. The complexity of these datasets requires the integration of advanced bioinformatics tools and computational models to accurately capture the dynamic nature of tumor biology and inform treatment decisions.

Combination cancer therapies (CCTs) have emerged as a promising approach to overcoming drug resistance and enhancing treatment efficacy. By integrating different therapeutic modalities, such as chemoimmunotherapy and chemoradiotherapy, CCTs aim to target multiple pathways and mechanisms of resistance simultaneously, offering a more comprehensive strategy for managing MPLCs [25]. The development of effective combination therapies, however, is contingent upon a deep understanding of the molecular pathways driving tumor progression and resistance [15].

5 Immunotherapy

In recent years, immunotherapy has emerged as a groundbreaking approach in the treatment of multiple primary lung cancers (MPLCs), fundamentally altering the therapeutic landscape. This section will explore the various types of immunotherapies currently available, highlighting their mechanisms of action and clinical implications. Understanding these diverse modalities is essential for appreciating their potential impact on patient outcomes and the ongoing evolution of treatment strategies in oncology.

5.1 Types of Immunotherapies

Immunotherapy has revolutionized the treatment landscape for multiple primary lung cancers (MPLCs) by harnessing the body's immune system to target and eliminate cancer cells more effectively than traditional therapies. This therapeutic approach incorporates a diverse range of modalities, including precision medicine strategies that consider individual genetic variations, advanced imaging techniques like photoacoustic imaging for noninvasive monitoring and treatment, and continuous optimization of therapeutic interventions. Each modality operates through distinct mechanisms of action and is applied in various clinical contexts, ultimately aiming to enhance personalized patient care by integrating diagnostic, therapeutic, and technological advancements. [35, 26, 27]

One of the most prominent forms of immunotherapy is immune checkpoint inhibitors, which have transformed the management of non-small cell lung cancer (NSCLC). These inhibitors work by blocking proteins that suppress immune cell activity, thereby enhancing the body's ability to recognize and destroy cancer cells. Notable examples include inhibitors targeting the programmed cell death protein 1 (PD-1) and its ligand PD-L1, which have shown significant efficacy in treating NSCLC . The clinical success of PD-1 and PD-L1 inhibitors, such as pembrolizumab and nivolumab, underscores the potential of these agents to improve patient outcomes by reactivating the immune system to target cancer cells [25].

In addition to immune checkpoint inhibitors, other promising immunotherapy approaches have emerged, including adoptive cell transfer therapies. Chimeric antigen receptor (CAR) T-cell therapy, a novel class of immunotherapy, involves the genetic modification of a patient's T cells to recognize and attack cancer cells, offering a highly personalized treatment strategy [25]. The success of CAR T-cell therapy in hematological malignancies has spurred interest in its application to solid tumors, including multiple primary lung cancers (MPLCs).

Moreover, the use of cancer vaccines represents another promising avenue in immunotherapy. These vaccines are designed to stimulate the immune system to recognize and target cancer cells, potentially enhancing the efficacy of other treatment modalities [25]. The integration of cancer vaccines with immune checkpoint inhibitors and other therapies is an area of active research, with the aim of enhancing therapeutic efficacy and overcoming resistance mechanisms [9].

The development and application of these diverse immunotherapeutic approaches have significantly expanded the treatment landscape for multiple primary lung cancers (MPLCs), offering new hope for patients with this complex condition. As our understanding of the complex molecular pathways and mechanisms driving lung cancer advances, the incorporation of immunotherapies into personalized treatment strategies will be crucial for enhancing clinical outcomes. This evolution is supported by recent findings that highlight the effectiveness of immunotherapeutic approaches, such as checkpoint inhibitors and therapeutic vaccines, in eliciting sustained responses in diverse patient populations. Additionally, the development of precision oncology, which tailors treatment based on the unique genetic profiles of tumors, underscores the importance of integrating both targeted therapies and immunotherapies to overcome treatment resistance and improve patient survival rates in lung cancer management. [28, 25, 38, 45]

5.2 Mechanisms of Action

Immunotherapy has emerged as a transformative approach in the treatment of multiple primary lung cancers (MPLCs), primarily through its ability to harness the body's immune system to target and eliminate cancer cells. A comprehensive understanding of the mechanisms underlying various immunotherapies is essential for optimizing their clinical application, enhancing treatment efficacy, and ultimately improving patient outcomes, particularly in light of challenges such as immune system modulation, adverse effects, and resistance to therapy. Advanced delivery technologies, such as nanoparticles and T cell-based systems, may play a pivotal role in enhancing the potency of these therapies while minimizing toxicity, thereby facilitating more effective integration of immunotherapy into cancer treatment regimens. [20, 21, 26, 9]

One of the key mechanisms of action in immunotherapy is the blockade of immune checkpoints, which are regulatory pathways that modulate immune responses. Immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) inhibitors and programmed death-ligand 1 (PD-L1) inhibitors, work by blocking the interaction between PD-1 on immune cells and PD-L1 on cancer cells . This blockade prevents cancer cells from evading immune detection and destruction, allowing the immune system to mount a more effective anti-tumor response [51].

In addition to immune checkpoint inhibitors, other immunotherapeutic approaches, such as adoptive cell transfer therapies, have shown promise in the treatment of MPLCs. Chimeric antigen receptor (CAR) T-cell therapy, for example, involves the genetic modification of a patient's own T cells to recognize and attack cancer cells, offering a highly personalized approach to cancer treatment [25]. This approach has demonstrated significant clinical benefits, particularly in hematological malignancies, and is being explored for its potential application to solid tumors, including MPLCs.

Combination strategies that integrate immunotherapy with other treatment modalities, including chemotherapy, radiation therapy, and targeted therapy, have demonstrated significant potential in improving therapeutic outcomes and addressing resistance mechanisms in cancer treatment. These approaches leverage a comprehensive understanding of the immune system's role in tumor response, as evidenced by the recent approval of various combination therapies by the US Food and Drug Administration (FDA) and ongoing clinical trials that explore innovative combinations and biomarkers for enhanced efficacy. [20, 52]. By leveraging the complementary mechanisms of action of different therapies, these combination strategies aim to optimize treatment outcomes and improve patient survival.

5.3 Mechanisms of Action

Immunotherapy has revolutionized the treatment landscape for multiple primary lung cancers (MPLCs) by leveraging the body's immune system to target and eliminate cancer cells. The mechanisms of action of various immunotherapies are multifaceted, encompassing the modulation of immune checkpoints to enhance anti-tumor responses, the improvement of antigen presentation to stimulate a more robust immune recognition of cancer cells, and the activation of immune effector cells such as T cells and natural killer cells, all of which work synergistically to overcome tumor-induced immune evasion and promote effective cancer treatment. [20, 21, 52, 53]

One of the most well-established mechanisms of action in immunotherapy is the blockade of immune checkpoints, which are regulatory pathways that cancer cells exploit to evade immune detection. Immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) inhibitors and

AI-generated, for reference only.

programmed death-ligand 1 (PD-L1) inhibitors, work by blocking the interaction between PD-1 and PD-L1, thereby reactivating the immune system to target and destroy cancer cells . These inhibitors have demonstrated significant clinical efficacy in the treatment of non-small cell lung cancer (NSCLC), leading to improved progression-free survival and overall response rates [54].

Additionally, the use of chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising approach in the treatment of multiple primary lung cancers (MPLCs). CAR T-cell therapy involves the genetic modification of a patient's own T cells to recognize and attack cancer cells, offering a highly personalized and targeted approach to cancer treatment [25]. This approach has shown significant clinical benefits in hematological malignancies and is being explored for its potential application to solid tumors, including MPLCs.

Combination strategies that integrate immunotherapy with other treatment modalities, such as chemotherapy and targeted therapy, represent a promising avenue for enhancing treatment efficacy and overcoming resistance mechanisms [25]. These combination strategies aim to harness the full potential of the immune system to target and eliminate cancer cells while minimizing damage to healthy tissues.

5.4 Mechanisms of Action

5.5 Clinical Outcomes and Challenges

5.6 Combination Strategies

5.7 Mechanisms of Action

Immunotherapy has emerged as a pivotal advancement in the treatment of multiple primary lung cancers (MPLCs), offering a novel approach by leveraging the body's immune system to target and eliminate cancer cells. The fundamental principle of immunotherapy involves amplifying the body's inherent immune response to effectively identify and eliminate cancer cells, which frequently escape immune detection through various adaptive mechanisms. This approach leverages the body's own immune system to combat a wide range of cancer types, utilizing advanced techniques such as immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and monoclonal antibodies. Recent advancements in the field have demonstrated that by understanding and targeting the specific pathways cancer cells use to evade immune surveillance, immunotherapy can lead to sustained therapeutic responses and improved outcomes for patients previously deemed incurable. [38, 55, 20, 21, 22]

A pivotal advancement in the field of cancer treatment is the emergence of immune checkpoint inhibitors, which have transformed immunotherapy by targeting specific pathways that cancer cells exploit to evade the immune response, thereby enabling long-term remission and survival in patients with previously untreatable metastatic cancers. [53, 52, 20, 21, 22]. These agents target specific proteins, such as programmed cell death protein 1 (PD-1) and its ligand PD-L1, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). By blocking these checkpoints, the immune system's ability to detect and attack cancer cells is restored, leading to improved clinical outcomes for patients with multiple primary lung cancers (MPLCs) . However, a subset of patients with MPLCs, particularly those with tumors exhibiting high levels of immune evasion, may not respond to monotherapy with checkpoint inhibitors. This challenge has prompted the development of combination strategies that integrate immunotherapy with other treatment modalities.

One promising approach to enhance the efficacy of immunotherapy is the combination with antiangiogenic therapies. This strategy aims to normalize the tumor vasculature, thereby improving immune cell infiltration and enhancing the overall antitumor immune response [9]. By normalizing the tumor microenvironment, antiangiogenic therapies can alleviate hypoxia and improve the delivery of immune cells and therapeutic agents to the tumor site, ultimately enhancing the effectiveness of immunotherapy in treating MPLCs.

The development of chimeric antigen receptor (CAR) T-cell therapy marks a transformative milestone in immuno-oncology, significantly enhancing treatment options for patients with various hematological malignancies, such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma, and paving the way for ongoing research aimed at extending its efficacy to solid tumors and other cancer types. [21, 56, 54]. CAR T-cell therapy involves the genetic modification of a patient's T cells to express chimeric antigen receptors that specifically target tumor-associated antigens, enabling the immune system to recognize and eliminate cancer cells more effectively . This innovative approach has shown promising results in hematological malignancies and is being actively explored for its potential application in solid tumors, including MPLCs.

The integration of immunotherapy with other treatment modalities, such as chemotherapy and targeted therapy, is a key strategy for enhancing therapeutic efficacy and overcoming resistance mechanisms in MPLCs . By integrating diverse therapeutic strategies, clinicians can effectively target multiple molecular pathways implicated in tumor progression, which not only enhances patient outcomes but also mitigates the risk of developing treatment resistance. This approach is particularly vital given the inherent heterogeneity of tumors and the complex mechanisms that contribute to drug resistance, such as alterations in drug targets and microenvironmental adaptations. Moreover, advancements in precision oncology, driven by comprehensive genomic profiling, allow for tailored treatment plans that address the unique genetic landscape of each patient's cancer, further improving the efficacy of combination cancer therapies and ultimately leading to better survival rates. [45, 15]

5.8 Integration with Other Therapies

The integration of surgical resection strategies with other therapeutic modalities is a cornerstone in the management of multiple primary lung cancers (MPLCs). This approach aims to enhance treatment efficacy and improve patient outcomes by leveraging advancements in precision medicine, targeted therapy, and immunotherapy. The development of comprehensive datasets, such as those aimed at identifying and diagnosing lung nodules, plays a crucial role in advancing computer-aided diagnosis (CAD) methods, thereby enhancing precision medicine initiatives [1]. These datasets facilitate the development of robust algorithms that can accurately interpret complex medical images, which is essential for tailoring individualized treatment strategies.

Targeted therapies have evolved significantly, with research categorizing methodologies into distinct frameworks that underscore the progression of lung cancer treatments, particularly through molecular targeting [11]. Such frameworks enable clinicians to identify specific molecular pathways and genetic mutations that can be exploited for therapeutic gain, thereby customizing treatment plans to the unique molecular profile of each tumor. This approach is particularly relevant in MPLCs, where the heterogeneity of tumors necessitates precise and personalized interventions.

The integration of antiangiogenic therapies with cancer immunotherapy represents another frontier in modern oncology, aimed at enhancing therapeutic efficacy and overcoming immune evasion by tumors [9]. By addressing the abnormal vasculature and immunosuppressive microenvironment characteristic of many lung cancers, these combined strategies hold promise for improving the clinical outcomes of patients with MPLCs.

Moreover, the application of novel adaptive algorithms that leverage real-time data is pivotal in optimizing resource distribution across healthcare networks, thereby enhancing operational efficiency and ensuring that patients receive timely and appropriate care [17]. Such innovations are integral to the successful implementation of modern oncology approaches, as they facilitate the seamless integration of advanced therapeutic modalities into clinical practice.

The regenerative processes observed in normal tissue repair have also provided insights into how cancer cells might co-opt these mechanisms during tumor progression, suggesting potential therapeutic targets that could be exploited to disrupt tumor growth [18]. Understanding these processes further enriches the arsenal of strategies available to oncologists in the management of MPLCs, underscoring the importance of a multidisciplinary approach in modern cancer care.

5.9 Mechanisms of Resistance

The emergence of resistance to targeted therapies poses a significant obstacle in the management of multiple primary lung cancers (MPLCs), primarily due to the tumor's intratumoral heterogeneity and the diverse mechanisms employed by cancer cells to evade treatment. These mechanisms include the development of secondary mutations in target kinases, activation of alternative signaling pathways, and the existence of minimal residual disease cells that can adapt and evolve under therapeutic pressure. Consequently, a comprehensive understanding of these resistance drivers is essential for improving treatment strategies and enhancing patient outcomes in those affected by MPLCs.

AI-generated, for reference only.

[43, 57, 58, 15, 25]. Cancer cells can employ various mechanisms to evade the effects of targeted therapies, leading to treatment failure and disease progression . One of the primary mechanisms of resistance is the acquisition of secondary mutations in the targeted gene, which can restore the function of the protein and enable the tumor to continue growing despite treatment.

The emergence of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) is a well-documented example of this phenomenon. The development of the T790M mutation in the EGFR gene is a common resistance mechanism that reduces the efficacy of first-generation TKIs, necessitating the development of third-generation inhibitors like osimertinib to overcome this challenge [7]. The identification and characterization of resistance mechanisms are crucial for the development of next-generation targeted therapies that can effectively address the evolving landscape of tumor biology.

Cancer cells can develop resistance not only through secondary mutations in the target kinase domain but also by activating alternative signaling pathways, engaging in phenotypic transformations, and adapting to their microenvironment. These mechanisms contribute to the complexity of tumor heterogeneity, where a small subpopulation of cells may survive treatment and subsequently evolve new mutations, allowing them to dominate and thrive in a therapy-resistant tumor. Understanding these diverse resistance strategies is crucial for improving targeted therapies and managing drug resistance in cancer treatment. [15, 57]. The activation of bypass signaling pathways, such as the PI3K/AKT/mTOR and RAS-MAPK pathways, can compensate for the inhibition of the primary target, allowing tumor cells to maintain their proliferative and survival capabilities . This underscores the need for combination therapies that target multiple pathways simultaneously, thereby reducing the likelihood of resistance and improving treatment outcomes.

The immunosuppressive tumor microenvironment also plays a critical role in the development of resistance to targeted therapies and immunotherapies. By promoting immune evasion and tumor progression, the tumor microenvironment can significantly compromise the efficacy of therapeutic interventions . Strategies aimed at modulating the tumor microenvironment, such as the combination of antiangiogenic therapies with immunotherapy, have shown promise in enhancing immune response and overcoming resistance mechanisms [9].

5.10 Clinical Outcomes and Challenges

Immunotherapy has significantly transformed the treatment paradigm for multiple primary lung cancers (MPLCs) by harnessing the immune system to target and eradicate cancer cells. Immune checkpoint inhibitors, particularly those targeting programmed cell death protein 1 (PD-1) and its ligand PD-L1, have demonstrated substantial efficacy in improving survival rates and quality of life for patients with non-small cell lung cancer (NSCLC) . These therapies enhance the body's immune response by blocking inhibitory pathways that cancer cells use to evade immune detection, leading to improved clinical outcomes [25].

Despite the promising results of immunotherapies, several challenges persist in their application to MPLCs. A significant challenge is the variability in patient responses, which can be attributed to the heterogeneity of tumors and the complex interplay between cancer cells and the immune system . The development of robust predictive biomarkers is essential for accurately identifying patient sub-populations that are most likely to benefit from specific therapies, thereby enhancing treatment efficacy and minimizing wasted resources in clinical trials. This process not only facilitates the optimization of therapeutic interventions but also aids in the continuous refinement of treatment strategies based on individual genetic and phenotypic profiles, ultimately supporting the goals of personalized and precision medicine. [26, 44, 59, 27]

The emergence of resistance to immunotherapy poses a significant challenge in cancer treatment, as it can result in treatment failure and accelerate disease progression, highlighting the need for ongoing research to identify predictive biomarkers and develop strategies to overcome this resistance. [38, 6, 19, 21, 22]. The immunosuppressive tumor microenvironment, characterized by a high mutation burden and complex tumor biology, can significantly compromise the efficacy of immunotherapies . Understanding the molecular and immunological mechanisms underlying resistance is essential for developing innovative strategies to overcome these barriers and improve therapeutic outcomes .

The development of combination strategies that integrate immunotherapy with other treatment modalities, such as targeted therapy and chemotherapy, represents a promising approach to enhancing

AI-generated, for reference only.

treatment efficacy and overcoming resistance mechanisms [25]. By targeting multiple pathways involved in tumor progression, these combination therapies aim to improve patient outcomes and reduce the likelihood of treatment resistance.

Furthermore, the integration of adaptive trial designs, such as group sequential clinical trials, offers a valuable tool for researchers in immuno-oncology [60]. These designs allow for interim analyses and modifications to the trial protocol, thereby enhancing the ability to detect treatment effects and improve clinical outcomes.

5.11 Combination Strategies

The treatment of multiple primary lung cancers (MPLCs) has been significantly advanced through the strategic integration of various therapeutic modalities, with combination strategies emerging as a cornerstone in modern oncology. These innovative approaches aim to significantly improve cancer treatment efficacy by simultaneously targeting multiple molecular pathways and addressing the various resistance mechanisms that frequently undermine the effectiveness of monotherapies. By leveraging advancements in precision oncology, which focuses on the genetic profiling of tumors to identify specific molecular alterations, these strategies facilitate the development of tailored therapies that account for the heterogeneity of tumors and the unique responses of individual patients. Furthermore, recent progress in drug delivery systems enhances the pharmacological properties of therapeutics, allowing for optimized administration of synergistic drug combinations while minimizing toxicity and overcoming pharmacological challenges. [43, 45]

One of the most promising combination strategies involves the integration of immunotherapy with targeted therapies, particularly those that target the epidermal growth factor receptor (EGFR) and RAS signaling pathways. This approach utilizes the synergistic potential of various therapeutic modalities, including immunotherapy, chemotherapy, and targeted therapies, to enhance the overall effectiveness of treatment for patients with metastatic and primary lung cancers (MPLCs). By combining these therapies, which operate through complementary mechanisms, the strategy aims to overcome resistance often encountered with single-agent treatments, thereby improving patient outcomes and increasing the likelihood of long-term remission. [20, 26]. Recent advancements in the development of RAS inhibitors have spurred interest in combining these agents with immunotherapy, as this combination has the potential to improve treatment outcomes by addressing the diverse mechanisms of resistance that characterize MPLCs .

The tumor microenvironment plays a crucial role in modulating immune responses and influencing treatment outcomes, making it a key focus in the development of combination strategies. The immunosuppressive nature of the tumor microenvironment can hinder the effectiveness of immunotherapies, necessitating the development of strategies to convert 'cold' tumors, which are less responsive to immunotherapy, into 'hot' tumors that are more susceptible to immune-mediated destruction [55]. Antiangiogenic therapies, which aim to normalize tumor vasculature and improve immune cell infiltration, represent one such strategy that has shown promise in enhancing the efficacy of immunotherapy [9].

Furthermore, the application of machine learning and artificial intelligence (AI) in the development of combination strategies is an emerging area of interest. These technologies have demonstrated the ability to enhance diagnostic accuracy and treatment personalization, leading to improved patient management [30]. By leveraging advanced algorithms, researchers can identify novel therapeutic targets and optimize treatment regimens, paving the way for more effective and personalized treatment strategies.

Future research should focus on developing targeted therapies, improving biomarker identification techniques, and exploring immunoprevention strategies to enhance treatment efficacy and reduce costs [19]. Additionally, the integration of multi-scale modeling approaches that include both cellular and molecular levels is crucial for addressing the complexity and heterogeneity of MPLCs [61]. By incorporating these models into the development of combination strategies, researchers can optimize treatment plans based on real-time patient data, ultimately improving patient outcomes and advancing the field of MPLC treatment [61].

AI-generated, for reference only.

6 Precision Medicine and Molecular Diagnostics

6.1 Precision Medicine and Molecular Diagnostics

Molecular diagnostics are crucial in managing multiple primary lung cancers (MPLCs) by enabling precise characterization of tumors' genetic and molecular features, essential for developing personalized treatment strategies. Techniques like liquid biopsy, which analyzes circulating tumor cells and DNA, offer non-invasive tumor monitoring, enhancing precision medicine's effectiveness in lung cancer management, especially in non-small-cell lung cancer (NSCLC), where understanding resistance mechanisms is vital [35, 7]. Liquid biopsies provide real-time insights, allowing clinicians to adapt treatments in response to emerging resistance.

The integration of comprehensive datasets and innovative methodologies, such as the DIVERSE framework, enhances precision medicine by combining diverse datasets like drug similarity, gene expression, and drug-target interactions. This approach improves predictive accuracy for drug responses, particularly in challenging out-of-matrix predictions, addressing the critical need for effective computational models amidst heterogeneous biological data [41, 62, 63]. Machine learning (ML) and artificial intelligence (AI) further transform molecular diagnostics by offering sophisticated tools for analyzing complex medical data, exemplified by the Maximum Entropy Method and the Functional Individualized Treatment Regimes with Imaging features (FITRI) method, which enhance clinical outcome predictions through spatial distribution analysis of immune cells and integration of imaging data with patient characteristics, respectively [31, 30].

Next-generation sequencing (NGS) facilitates comprehensive genomic analysis, enabling the identification of sequencing-matched therapies tailored to tumors' unique molecular characteristics [59]. However, challenges like distinguishing somatic mutations from germline variants and sequencing errors remain significant barriers [64]. In MPLCs, molecular diagnostics enhance personalized oncology by identifying specific genetic alterations and biomarkers, facilitating tailored treatment strategies that address cancer's complexity and heterogeneity [28, 45, 27].

The continuous advancement of molecular diagnostics, including the application of advanced diagnostic tools, ML, and AI technologies, enhances the precision and efficacy of cancer treatment, ultimately improving patient outcomes and advancing oncology.

6.2 Machine Learning and AI in Precision Medicine

Machine learning (ML) and artificial intelligence (AI) are revolutionizing precision medicine by enhancing diagnostic accuracy and informing therapeutic decisions through advanced data analysis. These technologies facilitate early detection, prognosis prediction, and personalized treatment strategies, transforming clinical practices by enabling effective patient stratification and improved outcomes through multi-omics and imaging technologies [65, 32, 30, 12].

Bayesian adaptive enrichment design (BAED) exemplifies these advancements by incorporating model uncertainty and allowing flexible biomarker-treatment effect relationships, optimizing treatment strategies based on real-time data, particularly in heterogeneous tumors like lung cancer [66]. The CF-HistoGAN framework showcases ML's potential in precision medicine by providing insights into tumor biology and informing personalized treatment plans [67]. AI-driven algorithms enhance diagnostic accuracy and therapeutic precision by leveraging high-dimensional datasets and advanced ML algorithms, optimizing treatment regimens, and transforming cancer care into a more personalized and efficient practice [32, 26].

The DIVERSE framework highlights data integration's power, improving disease prediction and treatment tailoring based on MPLCs' unique molecular profiles [62]. The uniCATE procedure enhances precision by assessing biomarkers' importance for predicting treatment effects, crucial in MPLCs due to tumor heterogeneity [13]. Despite advancements, challenges like complex statistical models and better integration of ML tools with inferential statistics remain [68]. Addressing these challenges is vital for maximizing precision medicine's potential in lung cancer treatment.

6.3 Innovative Methodologies and Frameworks

Innovative methodologies and frameworks are crucial for advancing precision medicine in lung cancer treatment, enhancing diagnostic accuracy and therapeutic efficacy through personalized strategies

AI-generated, for reference only.

considering genetic profiles and disease characteristics. Techniques like liquid biopsy enable real-time tumor monitoring, essential for adapting treatment strategies in MPLCs [5]. Integrating genomics, proteomics, microbiomics, and clinical data, powered by AI, further enhances precision in cancer treatment [67].

Advanced ML algorithms processing multi-omics data aim to improve findings' generalizability across diverse populations and optimize immunotherapy strategies, enhancing cancer treatments' efficacy [30]. Frameworks like the multi-view Bayesian mixture model facilitate identifying multiple clustering structures, essential for accurately capturing tumor complexity [13]. The MINDS platform exemplifies data integration advancements, supporting personalized treatment strategies by seamlessly integrating diverse data types into a cohesive system [41].

Bayesian neural networks (BNNs) in molecular diagnostics enhance mutation detection robustness by providing confidence measures for predictions, crucial for ensuring diagnostic and therapeutic decisions' accuracy in MPLCs. Developing innovative methodologies and frameworks is essential for advancing precision medicine approaches in lung cancer treatment, enabling more accurate disease prediction and treatment personalization through multi-scale modeling approaches [13].

6.4 Challenges and Future Directions in Precision Medicine

Implementing precision medicine in MPLCs faces challenges and opportunities for future advancement. Lung cancer's inherent complexity and heterogeneity, characterized by diverse genetic mutations and molecular profiles, impact treatment efficacy and patient outcomes [47]. These challenges necessitate advanced diagnostic and therapeutic strategies addressing drug resistance and tumor heterogeneity.

Comprehensive multi-omics datasets and advanced data processing frameworks, such as the DIVERSE framework, offer promising approaches to overcome these challenges. By integrating various datasets, the DIVERSE framework improves modeling intricate interactions among genetic, environmental, and clinical factors, enhancing disease prediction accuracy and treatment personalization [26, 62, 42, 36]. This approach is particularly relevant for MPLCs, where tumor heterogeneity requires precise and continuous monitoring to optimize treatment strategies.

Addressing cost barriers is crucial to ensuring access to effective treatments, regardless of financial circumstances [6]. Future research should focus on developing cost-effective diagnostic and therapeutic approaches, exploring novel therapeutic targets, and standardizing definitions for actionable mutations to enhance precision medicine in lung cancer treatment [14, 11]. The successful implementation of precision medicine in MPLC treatment hinges on developing intuitive health monitoring technologies and advanced data analytics, essential for enhancing disease prediction and optimizing treatment strategies. Addressing privacy concerns is vital for advancing precision medicine initiatives, with future research focusing on optimizing encryption methods to reduce computational costs and enhance patient privacy protection [39].

7 Challenges and Future Directions

Addressing the complexities of multiple primary lung cancers (MPLCs) requires understanding the multifaceted challenges of treatment resistance and tumor heterogeneity. The diverse cellular populations within tumors exhibit varying therapeutic responses, necessitating comprehension of resistance mechanisms to develop effective strategies. The following subsection explores intra-tumor heterogeneity's implications on treatment outcomes, emphasizing the need for advanced diagnostics and personalized treatments targeting cancer cell subpopulations in MPLCs.

7.1 Intra-tumor Heterogeneity and Treatment Resistance

Intra-tumor heterogeneity complicates MPLC management by fostering treatment resistance. This heterogeneity includes diverse cancer cell subpopulations within a tumor, each with distinct genetic and phenotypic traits [8]. Such diversity results in varied therapeutic responses, allowing certain subclonal populations to inherently possess or acquire resistance mechanisms, leading to treatment survival and disease progression [25]. The complexity of biological systems, data heterogeneity, and the need for extensive training datasets often result in overfitting and misinterpretation, complicating the understanding and management of MPLC resistance mechanisms [69]. Traditional diagnostics frequently fail to capture tumor heterogeneity, resulting in suboptimal treatments. This underscores the necessity for advanced diagnostic tools that provide comprehensive tumor heterogeneity understanding, guiding personalized treatment decisions [70]. Cancer cell phenotypic plasticity allows immune response evasion, contributing to tumor relapse during immunotherapy. This adaptability challenges overcoming MPLC treatment resistance, as tumor cells modify characteristics to survive therapeutic interventions [25]. Integrating multimodal data sources, such as imaging and -omics data, is crucial for improving NSCLC patient outcomes by offering a comprehensive understanding of tumor biology and resistance mechanisms. Recent visualization advancements, like Cinematic Rendering, enhance anatomical understanding, providing insights into tumor subpopulation distribution and informing personalized treatment strategies [8]. These methodologies offer valuable insights into tumor biology, informing treatment strategies that account for tumor heterogeneity. Recognizing current methodology limitations, including data integration challenges and computational resource needs, is essential for advancing precision oncology [70]. By leveraging advanced diagnostics, machine learning, and adaptive methodologies, researchers and clinicians can develop more effective personalized treatment strategies, improving MPLC patient outcomes.

7.2 Data Integration and Computational Challenges

Precision medicine for MPLCs relies on integrating diverse data types and advanced computational methods. However, this integration presents significant challenges that must be addressed to fully harness precision oncology's potential. A primary challenge lies in integrating high-dimensional data from various sources, such as genomics, proteomics, and imaging, requiring sophisticated knowledge representation and reasoning frameworks [71]. The diverse and asynchronous nature of clinical time series data further complicates data integration and analysis [41]. Computational costs and numeric instability in high-dimensional survival analysis pose notable challenges in applying data integration and computational methods in cancer treatment. These issues can lead to overfitting and result misinterpretation, particularly with small sample sizes and heterogeneous datasets. Developing robust computational frameworks to efficiently manage and analyze complex datasets is crucial for advancing precision oncology and improving patient outcomes [70]. Overfitting risks and small sample size limitations highlight the need for comprehensive datasets to enhance machine learning model robustness and generalizability [30]. Advanced computational frameworks, like the MLE framework, maintain data privacy while enabling accurate machine learning predictions, representing a promising approach to overcoming these challenges and facilitating secure precision medicine collaborations. Vocabulary mismatches between physician queries and medical literature present significant barriers to effective data integration, exacerbated by the need for ranking algorithms prioritizing treatment-related publications to ensure clinicians access the most relevant information [26]. Addressing privacy concerns is another critical challenge in data integration for precision medicine. Developing comprehensive frameworks that facilitate data sharing and integration while ensuring patient privacy is essential for advancing precision medicine initiatives [39]. Future research should focus on optimizing encryption methods to reduce computational costs and enhance the framework's ability to protect patient privacy [59].

7.3 Immunotherapy and Tumor Microenvironment

The tumor microenvironment (TME) is pivotal in immunotherapy efficacy for MPLCs. This complex milieu comprises various cellular and molecular components, including immune cells, stromal cells, blood vessels, signaling molecules, and extracellular matrix, interacting with tumor cells to influence cancer progression and therapeutic response [25]. The TME's immunosuppressive nature often challenges immunotherapy effectiveness, inhibiting immune cell infiltration and function, facilitating tumor immune evasion [9]. A key TME mechanism affecting immunotherapy is immune checkpoint regulation, such as programmed cell death protein 1 (PD-1) and its ligand PD-L1. These checkpoints are often upregulated in the TME, suppressing T-cell activity and enabling cancer cell immune surveillance evasion [58]. Immune checkpoint inhibitors, blocking these pathways, show promise in overcoming TME immunosuppressive effects and enhancing anti-tumor immune responses [25]. Besides immune checkpoints, abnormal TME vasculature creates a hypoxic environment that impairs immune cell function and promotes tumor progression. Antiangiogenic therapies aimed at normalizing tumor vasculature have improved immune cell infiltration and enhanced immunotherapy efficacy [9]. Addressing vascular abnormalities could improve immunotherapy responses by promoting a more favorable immune microenvironment [25]. Understanding TME molecular and cellular mechanisms is crucial for developing novel therapeutic strategies that effectively modulate the immune landscape and improve MPLC immunotherapy responses.

7.4 Technological Innovations and Privacy Concerns

Technological innovations have significantly advanced diagnostic precision and therapeutic efficacy in MPLC treatment. Integrating machine learning and artificial intelligence (AI) in genomic analysis has been pivotal in advancing precision medicine, identifying novel therapeutic targets and optimizing treatment regimens [72]. These technologies facilitate complex medical data analysis, offering insights into MPLC molecular and genetic underpinnings, essential for developing personalized treatment strategies. However, rapid technological advancements raise privacy concerns. Addressing these challenges requires implementing technical solutions, such as data encryption and anonymization, alongside legal and ethical considerations, ensuring responsible genomic data use in cancer research and treatment [72]. Policy plays a critical role in adopting and implementing personalized medicine technologies. Effective policy frameworks can facilitate technological innovation integration into clinical practice, ensuring precision medicine advancements while safeguarding individual rights.

7.5 Future Research and Development Strategies

The future of MPLC treatment is poised for significant advancements through key research and development strategies. Enhancing precision medicine approaches by integrating multi-omics data and advanced computational models is a primary focus. The DIVERSE framework exemplifies diverse dataset integration, including drug similarity, gene expression, and drug-target interactions, enhancing drug response prediction accuracy. Future research should explore integrating additional data types, such as 3D drug structure data, and improving feature selection methods to optimize therapeutic precision and patient outcomes [62]. Developing novel therapeutic targets and combination therapies is another critical area for future research. Exploring new molecular targets, such as next-generation mTOR inhibitors, and developing combinatorial therapies leveraging multiple modalities hold promise for enhancing treatment efficacy and optimizing patient outcomes [47]. Integrating machine learning (ML) and AI technologies into precision medicine is crucial for advancing MPLC treatment. These technologies offer sophisticated tools for analyzing complex datasets and enhancing diagnostic precision and therapeutic decision-making [73]. Future research could explore extending methods such as the Functional Individualized Treatment Regimes with Imaging features (FITRI) to generalized regression models and multi-stage regimes, improving personalized treatment plans and therapeutic outcomes [74]. Addressing precision medicine's high costs, including advanced diagnostic tests and targeted therapies, is crucial for ensuring patient access to effective treatments, regardless of financial circumstances [69]. Developing adaptive trial designs, such as the TOP design and the Double Encoder Model, offers a promising avenue for improving clinical trial efficiency and robustness. These designs can incorporate model uncertainty and allow flexible relationships between biomarkers and treatment effects, leading to more robust conclusions in precision medicine, particularly in lung cancer [75]. Future research should focus on extending methods such as the Functional Individualized Treatment Regimes with Imaging features (FITRI) to generalized regression models and multi-stage regimes, improving personalized treatment plans and therapeutic outcomes [74]. Addressing privacy concerns is another critical aspect of future research in precision medicine. Developing comprehensive frameworks that facilitate data sharing and integration while ensuring patient privacy is essential for advancing precision medicine initiatives [9]. Future research should focus on optimizing encryption methods to reduce computational costs and enhance the framework's ability to protect patient privacy [59].

8 Conclusion

The evolving landscape of multiple primary lung cancers (MPLCs) treatment underscores the necessity of integrating diverse therapeutic strategies to address the inherent complexities and heterogeneity of these malignancies. This survey highlights the critical role of advanced treatment modalities, including surgical resection, targeted therapy, immunotherapy, precision medicine, and molecular diagnostics, in improving patient outcomes.

AI-generated, for reference only.

Surgical resection continues to be a cornerstone in MPLC management, with innovative techniques like image-guided surgery enhancing the precision and effectiveness of tumor removal, thereby reducing damage to healthy tissues. The synergistic use of surgical resection alongside targeted therapies and immunotherapies is crucial for managing the diverse biological characteristics of MPLCs and optimizing therapeutic outcomes.

Targeted therapies have notably advanced MPLC treatment by focusing on specific molecular pathways and genetic alterations within tumors. The introduction of tyrosine kinase inhibitors (TKIs) and agents targeting pathways such as PI3K/AKT/mTOR and RAS-MAPK has significantly improved treatment efficacy and patient prognosis. However, the development of resistance mechanisms, including secondary mutations and alternative signaling pathways, poses ongoing challenges to the sustained effectiveness of these therapies.

Immunotherapy has similarly revolutionized MPLC management by harnessing the immune system to recognize and eliminate cancer cells. The use of immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors, has demonstrated substantial clinical success in enhancing survival rates and quality of life for patients with non-small cell lung cancer (NSCLC). Despite these successes, the immunosuppressive tumor microenvironment and variability in patient responses remain significant barriers to the efficacy of immunotherapies.

The integration of modern oncology approaches, including targeted therapies, immunotherapies, and precision medicine, is essential for refining treatment strategies and improving outcomes for MPLC patients. The development of innovative frameworks and adaptive trial designs has enhanced the precision and effectiveness of cancer treatment, providing renewed hope for those affected by MPLCs. Additionally, the incorporation of machine learning and artificial intelligence in precision medicine has transformed the field, facilitating the integration of diverse data types and the development of personalized treatment plans.

Despite these advancements, challenges persist in MPLC treatment, such as tumor heterogeneity, data integration issues, and privacy concerns. Overcoming these obstacles is crucial for unlocking the full potential of precision medicine in transforming lung cancer treatment. Future research should focus on refining methodologies, identifying novel therapeutic targets, and advancing efficient data integration and privacy-preserving technologies.

AI-generated, for reference only.

References

[1] Muwei Jian, Haoran Zhang, Mingju Shao, Hongyu Chen, Huihui Huang, Yanjie Zhong, Changlei Zhang, Bin Wang, and Penghui Gao. A cross spatio-temporal pathology-based lung nodule dataset, 2024.

[2] Jiancheng Yang, Mingze Gao, Kaiming Kuang, Bingbing Ni, Yunlang She, Dong Xie, and Chang Chen. Hierarchical classification of pulmonary lesions: A large-scale radio-pathomics study, 2020.

[3] Summer S Han, Gabriel A Rivera, Martin C Tammemägi, Sylvia K Plevritis, Scarlett L Gomez, Iona Cheng, and Heather A Wakelee. Risk stratification for second primary lung cancer. *Journal of Clinical Oncology*, 35(25):2893–2899, 2017.

[4] Tatiana V Denisenko, Inna N Budkevich, and Boris Zhivotovsky. Cell death-based treatment of lung adenocarcinoma. *Cell death & disease*, 9(2):117, 2018.

[5] Wen Li, Ji-Bin Liu, Li-Kun Hou, Fei Yu, Jie Zhang, Wei Wu, Xiao-Mei Tang, Feng Sun, Hai-Min Lu, Jing Deng, et al. Liquid biopsy in lung cancer: significance in diagnostics, prediction, and treatment monitoring. *Molecular cancer*, 21(1):25, 2022.

[6] Narges Ramezani and Erfan Mohammadi. The role of public health in the fight against cancer: Awareness, prevention, and early detection, 2023.

[7] Shang-Gin Wu and Jin-Yuan Shih. Management of acquired resistance to egfr tki–targeted therapy in advanced non-small cell lung cancer. *Molecular cancer*, 17:1–14, 2018.

[8] Dorin Comaniciu, Klaus Engel, Bogdan Georgescu, and Tommaso Mansi. Shaping the future through innovations: From medical imaging to precision medicine, 2016.

[9] Dai Fukumura, Jonas Kloepper, Zohreh Amoozgar, Dan G Duda, and Rakesh K Jain. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nature reviews Clinical oncology*, 15(5):325–340, 2018.

[10] José M. Álvarez Castro. Gene-environment interaction in the era of precision medicine – fix the potholes or start building a new road?, 2020.

[11] Fred R Hirsch, Giorgio V Scagliotti, James L Mulshine, Regina Kwon, Walter J Curran, Yi-Long Wu, and Luis Paz-Ares. Lung cancer: current therapies and new targeted treatments. *The Lancet*, 389(10066):299–311, 2017.

[12] Fabian V. Filipp. Opportunities for artificial intelligence in advancing precision medicine, 2019.

[13] Paul D. W. Kirk, Filippo Pagani, and Sylvia Richardson. Bayesian outcome-guided multi-view mixture models with applications in molecular precision medicine, 2023.

[14] Sanjiv Sam Gambhir, T Jessie Ge, Ophir Vermesh, and Ryan Spitler. Toward achieving precision health. *Science translational medicine*, 10(430):eaao3612, 2018.

[15] Joseph Malinzi, Kevin Bosire Basita, Sara Padidar, and Henry A. Adeola. Prospect for application of mathematical models in combination cancer treatments, 2021.

[16] Kyle Duke, Eric B. Laber, Marie Davidian, Michael Newcomb, and Brian Mustanksi. Optimal treatment strategies for prioritized outcomes, 2024.

[17] Sanad Aburass, Osama Dorgham, and Jamil Al Shaqsi. A hybrid machine learning model for classifying gene mutations in cancer using lstm, bilstm, cnn, gru, and glove, 2024.

[18] Ashley M Laughney, Jing Hu, Nathaniel R Campbell, Samuel F Bakhoum, Manu Setty, Vincent-Philippe Lavallée, Yubin Xie, Ignas Masilionis, Ambrose J Carr, Sanjay Kottapalli, et al. Regenerative lineages and immune-mediated pruning in lung cancer metastasis. *Nature medicine*, 26(2):259–269, 2020.

[19] C Lee Ventola. Cancer immunotherapy, part 3: challenges and future trends. *Pharmacy and Therapeutics*, 42(8):514, 2017.

[20] Shaoming Zhu, Tian Zhang, Lei Zheng, Hongtao Liu, Wenru Song, Delong Liu, Zihai Li, and Chong-xian Pan. Combination strategies to maximize the benefits of cancer immunotherapy. *Journal of hematology & oncology*, 14(1):156, 2021.

[21] Rachel S Riley, Carl H June, Robert Langer, and Michael J Mitchell. Delivery technologies for cancer immunotherapy. *Nature reviews Drug discovery*, 18(3):175–196, 2019.

[22] Virginia Bayer, Beau Amaya, Diane Baniewicz, Colleen Callahan, Lisa Marsh, and Asia S McCoy. Cancer immunotherapy. *Clinical journal of oncology nursing*, 21(2), 2017.

[23] Lais Osmani, Frederic Askin, Edward Gabrielson, and Qing Kay Li. Current who guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (nsclc): Moving from targeted therapy to immunotherapy. In *Seminars in cancer biology*, volume 52, pages 103–109. Elsevier, 2018.

[24] Nikita Vladimirov and Or Perlman. Molecular mri-based monitoring of cancer immunotherapy treatment response, 2023.

[25] Min Yuan, Li-Li Huang, Jian-Hua Chen, Jie Wu, and Qing Xu. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Signal transduction and targeted therapy*, 4(1):61, 2019.

[26] Jiaming Qu and Yue Wang. A medical literature search system for identifying effective treatments in precision medicine, 2019.

[27] Dean Ho, Stephen R Quake, Edward RB McCabe, Wee Joo Chng, Edward K Chow, Xianting Ding, Bruce D Gelb, Geoffrey S Ginsburg, Jason Hassenstab, Chih-Ming Ho, et al. Enabling technologies for personalized and precision medicine. *Trends in biotechnology*, 38(5):497–518, 2020.

[28] Margaret Morash, Hannah Mitchell, Himisha Beltran, Olivier Elemento, and Jyotishman Pathak. The role of next-generation sequencing in precision medicine: a review of outcomes in oncology. *Journal of personalized medicine*, 8(3):30, 2018.

[29] Michael R Kosorok and Eric B Laber. Precision medicine. *Annual review of statistics and its application*, 6(1):263–286, 2019.

[30] Yawei Li, Xin Wu, Ping Yang, Guoqian Jiang, and Yuan Luo. Machine learning applications in lung cancer diagnosis, treatment and prognosis, 2022.

[31] Matteo Tortora, Ermanno Cordelli, Rosa Sicilia, Lorenzo Nibid, Edy Ippolito, Giuseppe Perrone, Sara Ramella, and Paolo Soda. Radiopathomics: Multimodal learning in non-small cell lung cancer for adaptive radiotherapy, 2022.

[32] Bhavneet Bhinder, Coryandar Gilvary, Neel S Madhukar, and Olivier Elemento. Artificial intelligence in cancer research and precision medicine. *Cancer discovery*, 11(4):900–915, 2021.

[33] Wenbo Sun, Dipesh Niraula, Issam El Naqa, Randall K Ten Haken, Ivo D Dinov, Kyle Cuneo, and Judy Jin. Precision radiotherapy via information integration of expert human knowledge and ai recommendation to optimize clinical decision making, 2022.

[34] Anshu Ankolekar, Sebastian Boie, Maryam Abdollahyan, Emanuela Gadaleta, Seyed Alireza Hasheminasab, Guang Yang, Charles Beauville, Nikolaos Dikaios, George Anthony Kastis, Michael Bussmann, Sara Khalid, Hagen Kruger, Philippe Lambin, and Giorgos Papanastasiou. Advancing oncology with federated learning: transcending boundaries in breast, lung, and prostate cancer. a systematic review, 2024.

[35] Colman Moore and Jesse V Jokerst. Strategies for image-guided therapy, surgery, and drug delivery using photoacoustic imaging. *Theranostics*, 9(6):1550, 2019.

[36] Xiaofei Chen. Analyses and concerns in precision medicine: A statistical perspective, 2024.

[37] Hisashi Saji, Morihito Okada, Masahiro Tsuboi, Ryu Nakajima, Kenji Suzuki, Keiju Aokage, Tadashi Aoki, Jiro Okami, Ichiro Yoshino, Hiroyuki Ito, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (jcog0802/wjog4607l): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *The Lancet*, 399(10335):1607–1617, 2022.

[38] Aritraa Lahiri, Avik Maji, Pravin D Potdar, Navneet Singh, Purvish Parikh, Bharti Bisht, Anubhab Mukherjee, and Manash K Paul. Lung cancer immunotherapy: progress, pitfalls, and promises. *Molecular cancer*, 22(1):40, 2023.

[39] Meng Wu, Yan Liu, Hongyu Kang, Si Zheng, Jiao Li, and Li Hou. Building a controlled vocabulary for standardizing precision medicine terms, 2018.

[40] Geoffrey S Ginsburg and Kathryn A Phillips. Precision medicine: from science to value. *Health affairs*, 37(5):694–701, 2018.

[41] Aakash Tripathi, Asim Waqas, Kavya Venkatesan, Yasin Yilmaz, and Ghulam Rasool. Building flexible, scalable, and machine learning-ready multimodal oncology datasets, 2023.

[42] Thomas Gaudelet, Noel Malod-Dognin, and Natasa Przulj. Integrative data analytic framework to enhance cancer precision medicine, 2020.

[43] Mandana T Manzari, Yosi Shamay, Hiroto Kiguchi, Neal Rosen, Maurizio Scaltriti, and Daniel A Heller. Targeted drug delivery strategies for precision medicines. *Nature Reviews Materials*, 6(4):351–370, 2021.

[44] Abbi Abdel-Rehim, Oghenejokpeme Orhobor, Gareth Griffiths, Larisa Soldatova, and Ross D. King. Personalised medicine: Establishing predictive machine learning models for drug responses in patient derived cell culture, 2024.

[45] Manish Kumar. Precision oncology, signaling pathways reprogramming and targeted therapy: A holistic approach to molecular cancer therapeutics, 2024.

[46] Lei Zhong, Yueshan Li, Liang Xiong, Wenjing Wang, Ming Wu, Ting Yuan, Wei Yang, Chenyu Tian, Zhuang Miao, Tianqi Wang, et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal transduction and targeted therapy*, 6(1):201, 2021.

[47] Tian Tian, Xiaoyi Li, and Jinhua Zhang. mtor signaling in cancer and mtor inhibitors in solid tumor targeting therapy. *International journal of molecular sciences*, 20(3):755, 2019.

[48] Fu Peng, Minru Liao, Rui Qin, Shiou Zhu, Cheng Peng, Leilei Fu, Yi Chen, and Bo Han. Regulated cell death (rcd) in cancer: key pathways and targeted therapies. *Signal transduction and targeted therapy*, 7(1):286, 2022.

[49] Amanda R Moore, Scott C Rosenberg, Frank McCormick, and Shiva Malek. Ras-targeted therapies: is the undruggable drugged? *Nature reviews Drug discovery*, 19(8):533–552, 2020.

[50] Sarah A Dugger, Adam Platt, and David B Goldstein. Drug development in the era of precision medicine. *Nature reviews Drug discovery*, 17(3):183–196, 2018.

[51] Xing Jiang, Li Ren, Peyton Tebon, Canran Wang, Xingwu Zhou, Moyuan Qu, Jixiang Zhu, Haonan Ling, Shiming Zhang, Yumeng Xue, et al. Cancer-on-a-chip for modeling immune checkpoint inhibitor and tumor interactions. *Small*, 17(7):2004282, 2021.

[52] Timothy A Yap, Eileen E Parkes, Weiyi Peng, Justin T Moyers, Michael A Curran, and Hussein A Tawbi. Development of immunotherapy combination strategies in cancer. *Cancer discovery*, 11(6):1368–1397, 2021.

[53] Jezabel Varadé, Susana Magadán, and África González-Fernández. Human immunology and immunotherapy: main achievements and challenges. *Cellular & molecular immunology*, 18(4):805–828, 2021.

[54] Stephan Kruger, Matthias Ilmer, Sebastian Kobold, Bruno L Cadilha, Stefan Endres, Steffen Ormanns, Gesa Schuebbe, Bernhard W Renz, Jan G D'Haese, Hans Schloesser, et al. Advances in cancer immunotherapy 2019–latest trends. *Journal of Experimental & Clinical Cancer Research*, 38:1–11, 2019.

[55] K Esfahani, L Roudaia, N al Buhlaiga, SV Del Rincon, N Papneja, and WH Miller. A review of cancer immunotherapy: from the past, to the present, to the future. *Current Oncology*, 27(s2):87–97, 2020.

[56] Darrell J Irvine and Eric L Dane. Enhancing cancer immunotherapy with nanomedicine. *Nature Reviews Immunology*, 20(5):321–334, 2020.

[57] Zuan-Fu Lim and Patrick C Ma. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. *Journal of hematology & oncology*, 12(1):134, 2019.

[58] Charles M Rudin, Elisabeth Brambilla, Corinne Faivre-Finn, and Julien Sage. Small-cell lung cancer. *Nature Reviews Disease Primers*, 7(1):3, 2021.

[59] Philippe Boileau, Nina Ting Qi, Mark J. van der Laan, Sandrine Dudoit, and Ning Leng. A flexible approach for predictive biomarker discovery, 2022.

[60] Dominic Magirr and José L. Jiménez. Design and analysis of group-sequential clinical trials based on a modestly-weighted log-rank test in anticipation of a delayed separation of survival curves: A practical guidance, 2021.

[61] Jayanth Pratap. An optimal control strategy for mathematically modeling cancer combination therapy, 2021.

[62] Betül Güvenç Paltun, Samuel Kaski, and Hiroshi Mamitsuka. Diverse: Bayesian data integrative learning for precise drug response prediction, 2021.

[63] Kevin M Boehm, Pegah Khosravi, Rami Vanguri, Jianjiong Gao, and Sohrab P Shah. Harnessing multimodal data integration to advance precision oncology. *Nature Reviews Cancer*, 22(2):114–126, 2022.

[64] Geoffroy Dubourg-Felonneau, Omar Darwish, Christopher Parsons, Dami Rebergen, John W Cassidy, Nirmesh Patel, and Harry W Clifford. Safety and robustness in decision making: Deep bayesian recurrent neural networks for somatic variant calling in cancer, 2019.

[65] William Briguglio, Parisa Moghaddam, Waleed A. Yousef, Issa Traore, and Mohammad Mamun. Machine learning in precision medicine to preserve privacy via encryption, 2021.

[66] Lara Maleyeff, Shirin Golchi, Erica E. M. Moodie, and Marie Hudson. An adaptive enrichment design using bayesian model averaging for selection and threshold-identification of tailoring variables, 2024.

[67] Ghizal fatima, Risala H. Allami, and Maitham G. Yousif. Integrative ai-driven strategies for advancing precision medicine in infectious diseases and beyond: A novel multidisciplinary approach, 2023.

[68] Daniel J. Luckett, Eric B. Laber, and Michael R. Kosorok. Estimation and optimization of composite outcomes, 2020.

[69] Lana X Garmire. Strategies to integrate multi-omics data for patient survival prediction, 2020.

[70] Manlio De Domenico, Luca Allegri, Guido Caldarelli, Valeria d'Andrea, Barbara Di Camillo, Luis M. Rocha, Jordan Rozum, Riccardo Sbarbati, and Francesco Zambelli. Challenges and opportunities for digital twins in precision medicine: a complex systems perspective, 2024.

[71] Marco Scutari. Personalised medicine: Taking a new look at the patient, 2014.

[72] Chloé-Agathe Azencott. Machine learning and genomics: precision medicine vs. patient privacy, 2018.

[73] Jing Liang, Zhuo Hu, Zong-Wei Li, Kang-Jia Qiao, and Wei-Feng Guo. Multi-objective optimization based network control principles for identifying personalized drug targets with cancer, 2023.

[74] Isabel González-Crespo, Antonio Gómez-Caamaño, Óscar López Pouso, John D. Fenwick, and Juan Pardo-Montero. A biomathematical model of tumor response to radioimmunotherapy with αpdl1 and αctla4, 2022.

[75] Xinyi Li and Michael R. Kosorok. Functional individualized treatment regimes with imaging features, 2023.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.

AI-generated, for reference only.