SECTION «MEDICAL SCIENCES»

OBESITY AS A MODIFIER OF THE COURSE AND TREATMENT OF NON-SMALL CELL LUNG CANCER

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Abstract. Obesity is a global epidemic with multifactorial metabolic, endocrine, and immune consequences. Recent years have witnessed increasing attention to the interplay between obesity and cancer, including lung cancer. While lung cancer has traditionally been associated with smoking and environmental exposures, metabolic comorbidities such as obesity are emerging as important modifiers of disease risk, progression, and therapeutic outcomes. The aim of this study was explore the pathophysiological mechanisms linking obesity to lung cancer development and progression, and critically evaluates the impact of obesity on the efficacy and safety of various treatment modalities, including surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapies. *Materials and Methods.* A narrative review of recent literature was conducted, encompassing mechanistic studies, clinical trials, and meta-analyses. Particular attention was paid to evidence from large cohorts and molecular studies elucidating the impact of adiposity, inflammation, immune dysregulation, and altered pharmacokinetics on lung cancer outcomes. *Results.* Obesity contributes to lung carcinogenesis through chronic systemic inflammation, adipokine imbalance, insulin resistance, and remodeling of the tumor microenvironment. These factors promote tumor proliferation, immune evasion, and resistance to apoptosis. At the same time, obesity may paradoxically be associated with improved survival in some treatment contexts, a phenomenon known as the obesity

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paradox. In surgical management of non-small cell lung cancer, obesity poses anesthetic and technical challenges, increases the risk of wound complications, and prolongs operative time. However, minimally invasive approaches (e.g., robotic surgery) can mitigate some of these risks. In radiotherapy, increased adipose tissue affects dose distribution and enhances the risk of chest wall toxicity and impaired healing. Obesity-related inflammation may also reduce radiosensitivity, though some patients maintain favorable outcomes. In chemotherapy, altered drug distribution and metabolism in obese individuals necessitate careful dosing. Sarcopenic obesity, characterized by low muscle mass and high fat mass, is particularly associated with worse outcomes. Despite theoretical risks, guidelines recommend using full weight-based dosing in obese patients when clinically appropriate. Immunotherapy with checkpoint inhibitors appears to benefit from obesity in many cases, with elevated BMI associated with better progression-free and overall survival. However, this benefit may be counterbalanced by increased immune-related adverse events, necessitating close monitoring. Targeted therapies, particularly EGFR and ALK inhibitors, are influenced by metabolic alterations. Obesity-related overexpression of FTO and enhanced lipid metabolism may contribute to resistance mechanisms. Furthermore, weight gain during therapy, particularly with ALK inhibitors, may alter pharmacokinetics and comorbidity burden, affecting treatment outcomes. *Conclusions.* Obesity significantly affects the biology, progression, and treatment response of lung cancer. It exerts both negative and, in specific scenarios, potentially protective effects. Clinical management of obese patients with lung cancer requires a personalized, multidisciplinary approach that incorporates body composition, metabolic status, and treatment-specific risks. Future research should focus on stratifying patients beyond BMI, utilizing metabolic, inflammatory, and molecular markers to optimize therapeutic strategies.

1. Introduction

The epidemiology of obesity and its association with the development of lung cancer is among the most pressing topics in contemporary medical science, intersecting the fields of epidemiology, metabolism, oncology, and global public health. Over recent decades, the epidemic of overweight and obesity has reached the scale of a global crisis. According to current

estimates, more than one billion people worldwide are living with obesity, significantly exceeding previous figures and reflecting long-term negative trends in population health [1]. This shift is multifaceted, as obesity is not merely an excess of body weight but a complex metabolic and immunological disorder that contributes to the development of chronic diseases, including cancer [2].

The immunometabolic disturbances characteristic of obesity are not only risk factors for autoimmune and metabolic disorders but also contribute to chronic low-grade inflammation, which creates a favorable environment for the initiation and progression of malignant processes [2; 3]. Shared pathophysiological mechanisms, such as adipokine imbalance, insulin resistance, and oxidative stress, facilitate malignant cellular transformation and the formation of a tumor-promoting microenvironment. At the same time, recent studies have shown that obesity may paradoxically play a dual role in oncology: while promoting carcinogenesis, it may also enhance the efficacy of certain types of antitumor immunotherapy [4]. This phenomenon is attributed to complex changes in the immune tumor microenvironment and the hyperactivation of specific immune pathways in response to immune checkpoint inhibitors.

Epidemiological data indicate that the prevalence of obesity is rapidly increasing across all age, socioeconomic, and geographic groups. Particularly alarming is the rise among children and adolescents, as elevated body mass index (BMI) at a young age is associated with a higher risk of persistent obesity in adulthood and the subsequent development of comorbid conditions. On a global scale, this contributes to a growing burden of metabolic diseases and places additional strain on healthcare systems [5: 6].

One of the most severe manifestations of the global oncological burden is lung cancer. Despite a decline in age-standardized mortality rates in several regions, the absolute number of lung cancer cases and related deaths continues to rise. In 2019, lung cancer was responsible for more than two million deaths worldwide – nearly double the number recorded in 1990. Particularly concerning is the increasing mortality rate among women, which has been attributed to changes in smoking patterns and other environmental exposures [7].

Obesity is increasingly recognized as a modifier of lung cancer risk and disease progression. Alterations in metabolic status associated with obesity may influence tumor biology and the response to treatment [8; 4]. Clinical studies further highlight the significance of obesity in surgical planning, as it is linked to an elevated risk of postoperative complications and adverse perioperative outcomes [9]. Moreover, changes in body weight and composition have been shown to correlate with survival outcomes in patients with metastatic disease [10].

Visceral obesity, in particular, has garnered attention as an independent prognostic factor for poor disease outcomes, distinguishing it from general elevations in BMI. Excess visceral adipose tissue has been shown to promote tumor progression, enhance the pro-inflammatory tumor microenvironment, and worsen treatment outcomes, thereby prompting a re-evaluation of the so-called "obesity paradox" in oncology [11; 12].

Contemporary approaches to addressing the obesity epidemic conceptualize it not merely as a matter of individual behavior but as a chronic, multifactorial disease with profound social, economic, and environmental determinants. This perspective necessitates a comprehensive response that includes public policy initiatives, educational campaigns, multidisciplinary clinical care, and patient-centered treatment strategies tailored to individual needs [13].

Thus, the convergence of epidemiological, pathophysiological, and clinical evidence underscores the critical role of obesity in the development and course of lung cancer. The aim of this study is to provide a systematic analysis of scientific literature on the impact of obesity on the pathogenesis, progression, and treatment outcomes of non-small cell lung cancer (NSCLC), with a particular focus on surgical, radiation, chemotherapy, immunotherapy, and targeted therapy contexts. To achieve this objective, relevant publications were identified and analyzed from the international scientific database PubMed, ensuring an evidence-based foundation for the conclusions presented.

2. Pathophysiological Mechanisms Linking Obesity to Lung Cancer Development

The increasing global prevalence of obesity necessitates a reevaluation of its consequences not only in the context of cardiometabolic disorders

but also in oncological pathology. Obesity has long been recognized as a multisystem disease characterized by metabolic dysregulation, chronic inflammation, hormonal imbalance, alterations in microbiota, and immune response. Crucially, the adipose microenvironment in individuals with obesity facilitates the activation of proto-oncogenic pathways, inactivation of tumor suppressors, and the creation of conditions conducive to the growth and metastasis of malignant cells, including lung cancer cells.

Chronic Inflammation and Immune Cascade Activation. In obese individuals, adipocytes undergo hypertrophy, resulting in increased expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and MCP-1. These molecules recruit immune cells, particularly macrophages, into adipose tissue. Under normal conditions, these macrophages exhibit an M2 (anti-inflammatory) phenotype; however, obesity drives a shift toward the M1 (pro-inflammatory) phenotype. This polarization initiates systemic low-grade chronic inflammation – a pathogenic driver of carcinogenesis [14–17]. Additionally, the activation of nuclear factor NF-κB regulates the transcription of genes associated with cell proliferation, angiogenesis, and apoptosis inhibition, all of which promote tumor formation. In lung cancer, chronic systemic inflammation contributes to epithelial-mesenchymal transition (EMT), invasion, and angiogenesis. According to Divella et al. [18], obesity increases cancer risk by 30–40%, primarily due to cytokine-induced malignant cell proliferation.

Hypoxia and Angiogenesis in Adipose Tissue. A less apparent but critical mechanism is local hypoxia within expanding adipose tissue. Rapid adipose tissue growth outpaces vascular adaptation, leading to reduced oxygenation. This activates hypoxia-inducible factor HIF-1α, which in turn promotes angiogenesis via vascular endothelial growth factor (VEGF), upregulates glycolytic gene expression, inhibits apoptosis, and supports cell survival under stress conditions [19]. In lung cancer, where hypoxia is a hallmark of the tumor microenvironment, HIF-1α activation fosters more aggressive tumor behavior, therapeutic resistance, and increased metastatic potential.

The Role of Adipokines: Leptin and Adiponectin. Adipose tissues secrete a wide array of biologically active substances (adipokines) that play pivotal roles in linking obesity with tumorigenesis. Among these, leptin and adiponectin are the most studied. In obese individuals, leptin levels can be four to six times higher than normal [20]. Leptin activates several

oncogenic signaling pathways, including JAK/STAT3, PI3K/Akt, and ERK/MAPK, which enhance cell proliferation, inhibit apoptosis, promote angiogenesis, and increase tumor cell invasiveness. A study by Mullen and Gonzalez-Perez [21] demonstrated that leptin promotes non-small cell lung cancer (NSCLC) cell growth through STAT3 activation and subsequent upregulation of VEGF and MMP9.

In contrast, adiponectin exhibits antitumor properties, and its levels are significantly reduced in individuals with obesity. Adiponectin activates AMP-activated protein kinase (AMPK), inhibits PI3K/Akt and mTOR signaling, suppresses NF-κB activity, reduces oxidative stress, and promotes apoptosis. Low adiponectin concentrations have been associated with an increased risk of breast, colorectal, and lung cancers [22]. A study by Nigro et al. [23] found that each 1 μg/mL decrease in adiponectin levels is associated with a 10–12% increase in the risk of malignancy.

Lipotoxicity and Oxidative Stress. Excess free fatty acids (FFAs), resulting from hyperactive lipolysis in adipocytes, induce lipotoxicity, insulin resistance, and the generation of reactive oxygen species (ROS), which damage DNA, lipids, and proteins. Capurso C. and Capurso A. [24] emphasized that FFAs upregulate Toll-like receptor 4 (TLR4) expression, thereby activating NF-κB and amplifying inflammation. Cavaliere et al. [25] demonstrated that disruption of lipid homeostasis within adipose tissue creates a metabolically adverse environment, which interacts with the liver, muscles, and lungs to increase the metastatic potential of tumors.

Role of Adipose Stromal Cells. Adipose-derived stromal cells possess the capacity to differentiate and secrete exosomes, growth factors, and proteolytic enzymes. In a study by Daquinag et al. [26], targeted depletion of adipose stromal cells using pro-apoptotic peptides resulted in a 40–60% reduction in tumor growth in mice, underscoring the active role of adipose tissue in shaping the oncogenic microenvironment. A review by Himbert et al. [27] supports the view that adipose tissue is not merely a passive reservoir but a dynamic milieu that, through paracrine signaling, influences tumor cell growth, survival, and invasiveness.

In summary, obesity fosters a pro-tumorigenic environment in lung cancer through multifactorial mechanisms, including chronic inflammation, endocrine dysfunction, hypoxia, oxidative stress, and adipokine imbalance. Understanding these pathophysiological links provides new opportunities

for personalized interventions, such as targeted therapies against leptin, adiponectin activation, modulation of the tumor microenvironment, and anti-inflammatory prevention strategies.

3. Impact of Obesity on Surgical Outcomes in Lung Cancer

Obesity, affecting an increasingly large proportion of the global population, significantly complicates the management of patients undergoing surgical interventions, particularly for lung cancer. While surgery remains the cornerstone of treatment for patients with early-stage NSCLC, excess body weight alters the clinical profile of these patients and affects the full spectrum of perioperative events – from anesthetic management to long-term survival outcomes.

Physiologically, obesity is associated with reduced functional residual lung capacity, increased airway resistance, and impaired ventilation-perfusion matching. These alterations elevate the risk of intraoperative hypoxia, which is especially relevant during thoracoscopic or open procedures performed in the lateral decubitus position with one-lung ventilation. According to Leonardi et al. [28], obese patients undergoing thoracoscopic lobectomy with one-lung ventilation were more likely to experience hypoxemic episodes requiring adjustments to the respiratory protocol. In such cases, standard ventilation strategies are often insufficient, necessitating individualized approaches, such as the application of higher positive end-expiratory pressure, more frequent repositioning, and optimization of oxygenation.

Overall, obesity tends to prolong surgical duration due to difficulties in visualizing anatomical structures and technical constraints. A systematic review by Wang et al. [29] found that the mean operative time was significantly longer in obese patients, with an average difference of 14.3 minutes. This extension in operative time is, in turn, associated with an increased risk of postoperative complications, such as infections, thromboembolic events, and bleeding. These risks are further exacerbated by the presence of comorbid metabolic conditions frequently observed in obese individuals, including type 2 diabetes mellitus, hypertension, and obstructive sleep apnea syndrome.

However, data on the actual impact of obesity on postoperative complications in lung cancer surgery remain conflicting. In many cases,

no significant increase in the overall complication rate has been observed in obese patients. For instance, Tong et al. [30], in a retrospective analysis of elderly patients, demonstrated that obesity did not significantly affect the incidence of postoperative pulmonary complications, length of hospital stay, or the need for intensive care. At the same time, other studies, such as that by Guerrera et al. [31], revealed a slightly higher frequency of intraoperative challenges in patients with morbid obesity, including technical difficulties and an increased rate of conversion from minimally invasive to open surgical approaches.

A key factor influencing clinical outcomes in the context of obesity is the type of surgical access. Video-assisted thoracoscopic surgery and robotic-assisted procedures are associated with lower complication rates, even in patients with high BMI. Specifically, in obese patients undergoing robotic anatomical resection, outcomes were superior to those following thoracoscopic surgery, with fewer thromboembolic events and reduced need for postoperative respiratory support. This underscores the importance of selecting the appropriate surgical technique for overweight patients, rather than relying solely on BMI-based risk stratification [32].

Another important consideration is the effect of obesity on wound healing. Excess adipose tissue impairs microcirculation, promotes chronic local inflammation, and alters the wound microenvironment architecture, thereby delaying granulation and epithelialization. As noted by Pierpont et al. [33], obese individuals face a 1.5–2-fold higher risk of wound dehiscence, surgical site infections, and seroma formation compared to patients with normal body weight. This is particularly relevant in thoracic surgeries, where the size of the incision and physiological strain on the chest wall are considerable.

One of the most intriguing and debated phenomena is the so-called "obesity paradox." In several studies, obese patients demonstrated not inferior but even improved postoperative survival outcomes. Alifano et al. [34], in a large French cohort, found that five-year survival after lung cancer resection was higher in patients with moderate obesity compared to those with normal BMI. Similarly, Lee et al. [35] reported that elevated BMI was associated with better overall postoperative survival, regardless of skeletal muscle mass. This could be attributed to greater energy reserves, improved

tolerance to metabolic stress, and potentially beneficial effects of certain adipokines on immune function.

In the context of lung cancer surgery, optimizing perioperative care for patients with obesity requires a multidisciplinary approach involving thoracic surgeons, anesthesiologists, dietitians, and physiotherapists. Preoperative risk stratification, individualized ventilation strategies, and attention to nutritional status are essential. While modern technologies from minimally invasive surgery to enhanced perioperative rehabilitation help mitigate the adverse effects of obesity, this issue warrants further investigation and standardization of care protocols.

4. Impact of Obesity on the Outcomes of Lung Cancer Radiotherapy

Obesity not only influences the risk and progression of lung cancer but also significantly modifies the outcomes of radiotherapy, which remains one of the primary modalities for local treatment of malignant neoplasms, including both non-small cell and small cell lung cancer. Radiotherapy is applied as a standalone therapy or in combination with surgery, chemotherapy, or immunotherapy to control the primary tumor, manage locoregional metastases, or provide palliative treatment in advanced stages. However, in patients with obesity, physical, metabolic, and technical factors pose serious challenges to the effective and safe delivery of radiation therapy [36].

One of the primary issues highlighted in clinical reviews is the technical complexity of achieving adequate radiation dose delivery in patients with significant excess body weight. Increased tissue thickness and altered adipose tissue distribution can lead to dose inhomogeneity within the tumor and increased exposure of adjacent healthy organs. This is due to the physical properties of radiation scattering and absorption in tissues of varying density, complicating precise treatment planning and dosimetric modeling. Specifically, in thick layers of adipose tissue, the target margins become less distinct, which raises the risk of tumor underdosage and inadvertent irradiation of healthy pulmonary parenchyma or cardiovascular structures. These technical limitations not only reduce the efficacy of local tumor control but may also increase the incidence of treatment-related toxicities [37; 38].

One of the most common adverse effects of radiotherapy in lung cancer treatment is chest wall and soft tissue pain in the irradiated area, with a higher incidence observed in obese patients. For example, the study by Welsh et al. [39] demonstrated that elevated BMI significantly increases the risk of chest wall pain following high-dose stereotactic body radiotherapy. In this study, obese patients experienced a 50–70% higher rate of severe pain symptoms associated with the impact of high fractional doses on soft tissues. This greatly complicates treatment tolerability and may necessitate dose reduction or interruptions in therapy planning.

In addition to the physical and technical aspects, obesity is accompanied by numerous metabolic and nutritional disturbances that may affect tumor response to radiotherapy and overall survival outcomes. Obese patients often exhibit obesity-related metabolic dysfunction, including estrogenic dysregulation, insulin resistance, and elevated systemic inflammatory markers, which collectively create a more aggressive tumor microenvironment. According to a study by Chen et al. [40], in patients with metastatic NSCLC undergoing combination treatment – radiotherapy alongside immunotherapy – the integrated assessment of metabolic factors and nutritional status emerged as an independent predictor of progression-free survival. A high total adipose tissue volume was associated with an increased risk of disease progression (hazard ratio [HR] = 2.81, P = 0.029), whereas a high prognostic nutritional index served as a favorable predictive marker (HR = 0.24, P < 0.001) for progression-free survival among patients receiving radiotherapy in combination with immune checkpoint inhibitors. This comprehensive body composition assessment, beyond the conventional BMI, allows for more precise prediction of therapeutic response to radiation, as nutritional status reflects not only fat mass but also muscle mass and overall metabolic reserve.

The predominance of visceral fat distribution in obese individuals is also associated with several adverse effects in the context of radiotherapy. Multiple studies have reported that it is the elevated volume of visceral adipose tissue – not BMI per se – that correlates with more aggressive tumor biology and lower radiosensitivity, resulting in poorer local control and higher rates of distant metastases. This phenomenon is attributed to the distinct metabolic profile of visceral fat, which includes secretion of pro-inflammatory cytokines, alteration of immune responses, and

modulation of the tumor microenvironment. These effects may impair the immunostimulatory potential of radiation-induced DNA damage in tumor cells, thereby reducing treatment efficacy [41].

Another critical factor is impaired healing of radiation-induced skin and subcutaneous tissue reactions. Obesity is known to negatively impact microcirculation and oxidative balance, delaying reparative mechanisms in irradiated tissues. Clinically, this often manifests as more pronounced dermatologic reactions and prolonged erythema after radiotherapy, necessitating more frequent treatment breaks or dose reductions to limit chronic toxicity [42].

A particularly relevant aspect in the era of multimodal cancer therapy is the interaction between radiotherapy and immunotherapy, which is increasingly used in patients with locally advanced or metastatic lung cancer. Here, obesity again plays a significant role: in combined treatment regimens involving radiotherapy and immune checkpoint inhibitors, patients with better nutritional status and moderate adipose mass demonstrated longer relapse-free survival compared to those with lower nutritional indices or higher visceral-to-subcutaneous fat ratios. Notably, a high visceral-to-subcutaneous adipose tissue ratio was identified as an independent negative prognostic factor for disease progression (HR = 5.53, P = 0.002), underscoring the importance of adipose tissue distribution analysis in predicting response to combined therapeutic approaches [40].

Despite the numerous challenges, some studies suggest that obesity is not always associated with worse survival outcomes following radiotherapy. The so-called “obesity paradox,” initially described in the context of surgical and systemic therapies, has also been observed by certain authors in relation to radiotherapy. In some patient cohorts with elevated BMI, improved overall and progression-free survival has been reported compared to patients with normal body weight. These observations may be attributed to factors such as greater metabolic reserve or a more robust response to DNA damage induced by radiation [40; 41]. However, such findings require further validation, as they may be influenced by population heterogeneity, comorbidities, and variations in radiation regimens.

Overall, obesity exerts a multifaceted influence on the outcomes of radiotherapy for lung cancer:

1. It complicates precise dosimetric planning and dose delivery.

2. It increases the risk of chest wall pain and local toxicity.

3. It exacerbates metabolic and immune dysfunctions that may affect tumor radiosensitivity.

4. It impairs tissue healing and amplifies radiation-induced skin reactions.

5. It modulates treatment response in combined regimens such as radiotherapy plus immunotherapy.

These factors underscore the need for an integrated clinical approach that considers individual patient body composition metrics – particularly fat and muscle distribution – rather than relying solely on BMI when planning radiotherapy. Tailoring radiotherapy protocols, implementing careful nutritional monitoring, and providing multidisciplinary care for obese patients may help optimize treatment outcomes and reduce toxicity.

Impact of Obesity on Chemotherapy Outcomes in Lung Cancer

Chemotherapy remains a cornerstone of comprehensive treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), commonly used in first-line settings or in combination with immunotherapy or targeted agents. Obesity, as a multisystemic disorder, significantly modifies the pharmacokinetics, pharmacodynamics, drug tolerability, and clinical outcomes of chemotherapy. These effects stem not only from increased body mass but also from alterations in metabolism, immune regulation, body composition, and fat distribution.

One of the primary challenges posed by obesity is its impact on chemotherapy dosing and pharmacological assessment. Traditionally, cytotoxic drug dosages are calculated based on body mass index (BMI) or body surface area (BSA). However, these approaches have notable limitations in patients with obesity. Excess adipose tissue alters the distribution of lipophilic and hydrophilic drugs, influences the volume of distribution, hepatic metabolism, and renal clearance. This complexity makes it difficult to predict the actual tissue concentration of active metabolites and may lead to either increased toxicity or reduced therapeutic efficacy [43; 44]. Therefore, modern international guidelines recommend avoiding automatic dose reductions based solely on BMI in obese patients unless specific contraindications exist. When possible, actual body weight should be used to calculate dose intensity, taking into account the clinical context and pharmacologic properties of the agents employed [45].

In NSCLC patients, obesity may influence the efficacy and safety profile of first-line chemotherapy, particularly with platinum-based regimens combined with other cytotoxic agents. For instance, a study by Kicken et al. [46] examined the association between BMI, treatment safety, and efficacy of platinum-based chemotherapy in patients with metastatic NSCLC. While no statistically significant differences in the incidence of severe toxic effects were observed between obese and normal-weight patients, the authors noted a trend toward reduced hematologic toxicity in patients with higher BMI. This could reflect altered drug distribution volumes and differential metabolic responses in adipose tissue. Such findings partially align with the concept of the obesity paradox, where increased body mass may be associated with protective physiological reserves or differential drug handling that could influence chemotherapy tolerance.

Impact of Obesity on Chemotherapy Outcomes in Lung Cancer

Previous studies, particularly cohort analyses of female lung cancer patients receiving carboplatin + paclitaxel combinations, have shown that although patients with obesity exhibited similar rates of organ-specific toxicities (such as hematologic and neurologic adverse events), they tended to have poorer overall survival compared to their normal-weight counterparts [47]. This may be due to metabolic alterations and the frequent co-occurrence of sarcopenia or sarcopenic obesity, which negatively impacts physiological reserve and the ability to tolerate cytotoxic agents.

Sarcopenia and sarcopenic obesity have gained increasing attention in evaluating the effectiveness of anticancer therapies. Wang et al. [48] demonstrated that in NSCLC patients undergoing immunotherapy or combined chemo-immunotherapy, the presence of sarcopenia or sarcopenic obesity was an independent negative prognostic factor for both progression-free and overall survival. In cohorts with sarcopenic obesity, the risk of disease progression was 34–42% higher, and the risk of death was 28–37% higher compared to those without this phenotype. These findings underscore the importance of body composition, rather than total body mass alone, in predicting post-chemotherapy outcomes.

A critical question in clinical practice is whether chemotherapy dosages should be adjusted for patients with obesity to improve therapeutic outcomes. Current recommendations, including those from

ASCO and various European oncology and endocrinology societies (AIOM/AMD/SIE/SIF), emphasize the use of full weight-based dosing for most cytotoxic agents unless clear contraindications or comorbidities exist. Dose reductions based solely on BMI may lead to subtherapeutic drug exposure, reduced efficacy, and diminished histologic response rates, including lower objective response rates and median survival. These guidelines caution against the routine practice of dose attenuation based on BMI, as it lacks strong evidence and may negatively impact outcomes [44; 45].

Obesity also affects the risk profile for chemotherapy-induced hematologic and cardiotoxic events. Patients with obesity and concurrent cardiovascular disease are at heightened risk, especially when treated with agents known for cardiotoxic potential or in high-dose regimens. Peer-reviewed evidence suggests that close monitoring of cardiac function and electrolyte balance, along with individualized dosing strategies that consider cardiovascular risk, are essential to minimize the danger of therapy-induced cardiac dysfunction, which can be life-threatening during repeated chemotherapy cycles [49].

Another important aspect of evaluating chemotherapy effectiveness in obesity is assessing body composition using modern technologies such as artificial intelligence and volumetric tissue analysis. Recent studies have shown that in NSCLC patients, parameters like muscle mass volume, adipose tissue distribution, and their interaction with agents such as metformin may predict not only toxicity but also therapeutic response. Specifically, obese patients with greater muscle mass demonstrated better drug tolerance and longer median survival compared to those with similar BMI but pronounced sarcopenia [50]. These data highlight that BMI alone provides an incomplete clinical picture, and that comprehensive body composition assessment can significantly enhance chemotherapy outcome prediction.

Overall, outcomes for patients with obesity receiving chemotherapy for lung cancer are heterogeneous. On one hand, obesity can modify the risk of toxic reactions and necessitate dose adjustments; on the other hand, with optimized dosing and support for organ function, patients can achieve outcomes comparable to or even better than those with normal weight. Recent evidence suggests that a personalized approach – taking into account

not just BMI but also detailed body composition and metabolic status – can substantially improve treatment responses and survival.

In conclusion, the impact of obesity on chemotherapy in lung cancer is multifaceted, encompassing pharmacokinetic and pharmacodynamic changes, toxicity modulation, influence of body composition on therapeutic response, and interactions with comorbidities. Further investigation using advanced body analysis tools and molecular biomarkers is critical for optimizing systemic therapy and improving survival in obese patients undergoing treatment for lung cancer.

5. Impact of Obesity on Immunotherapy in Lung Cancer

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has revolutionized the treatment landscape for locally advanced and metastatic NSCLC, offering prolonged responses and improved overall survival for a subset of patients. However, obesity, often associated with immune dysregulation, systemic inflammation, and metabolic dysfunctions, may modulate the effectiveness of immunotherapeutic approaches in both enhancing and attenuating their therapeutic outcomes.

Obesity is accompanied by complex changes in the immune system that directly impact antitumor immunity. These include elevated levels of proinflammatory cytokines and increased macrophage activation within adipose tissue, contributing to a chronic, low-grade inflammatory state. This environment can alter the functionality of immune mechanisms targeted by immunotherapy [51,52]. For instance, obesity has been linked to an increased population of functionally exhausted T lymphocytes, which may affect responsiveness to checkpoint blockade therapies such as anti–PD-1/PD-L1 and anti–CTLA-4 agents [53].

One of the most well-documented clinical observations is the so-called "obesity paradox" in immunotherapy, where patients with elevated BMI show improved responses to immune checkpoint inhibitors and better survival outcomes compared to normal-weight individuals. In a large meta-analysis, Zhang et al. [54] reported that among NSCLC patients treated with immunotherapy, those with higher BMI experienced significantly improved overall and progression-free survival. The relative risk of death was reduced by approximately 15–20% in the obese group compared to control groups ($p < 0.05$). These findings are consistent with the results of

Guo et al. [55], who, in a systematic review and meta-analysis, confirmed that obesity was an independent positive prognostic factor for response to checkpoint inhibitors across various solid tumors, including NSCLC.

Mechanistic studies offer several explanations for these clinical findings. Firstly, obesity appears to induce heightened activation of CD8+ T lymphocytes characterized by a distinct metabolic profile, including enhanced glycolysis and alterations in histone modification regulation, leading to a more potent antitumor response. Such changes may potentiate the efficacy of immunotherapy, as robust CD8+ T cell function is central to the success of PD-1/PD-L1 inhibition strategies [56].

These data suggest that, contrary to traditional assumptions, obesity may not always impair and may in some cases enhance the efficacy of immune checkpoint blockade in lung cancer. However, the precise mechanisms remain complex and multifactorial, and further research is essential to determine which patients are most likely to benefit from this paradoxical effect and how it might be leveraged in clinical practice.

Secondly, obesity modulates the tumor microenvironment through the secretion of adipokines and cytokines such as leptin, IL-6, and TNF-α, which influence immune cell function and may enhance their sensitivity to immune checkpoint blockade. This likely explains the clinical observation that obese patients often demonstrate longer durations of response to immunotherapy and a reduced risk of disease progression [57].

However, obesity is also associated with a heightened risk of immunotherapy-related adverse events, particularly severe immune-related toxicities. Georgakopoulou et al. [58] have outlined a spectrum of pulmonary complications linked to immune checkpoint inhibitors, including pneumonitis, which is particularly dangerous in patients with comorbid chronic conditions. The chronic inflammatory state associated with obesity, characterized by elevated baseline levels of inflammatory mediators, may exacerbate the severity of such immune-mediated reactions. Furthermore, metabolic abnormalities common in obesity, such as insulin resistance and dyslipidemia, can impair tolerance to checkpoint inhibitors and elevate the risk of immune-related toxicities involving the skin, gastrointestinal tract, and other organs [59].

In this context, it is important to recognize that the effectiveness of immunotherapy depends not only on general immune competence but also

on specific components of body composition and the patient's metabolic profile. The ratio of muscle mass to fat mass, as well as particular metabolic markers (e.g., cytokines, hormones), can influence therapeutic response independently of BMI alone [60]. For instance, patients with high adiposity but preserved muscle mass tend to show better responses to immune checkpoint inhibitors, whereas those with sarcopenia are more likely to experience disease progression and reduced overall survival.

Clinical data reinforce this complexity. A prospective study demonstrated that patients with elevated BMI (>30 kg/m²) who received checkpoint inhibitors had significantly higher objective response rates compared to those with BMI <25 kg/m² ($p < 0.01$), and a longer median overall survival (18 months vs. 12 months). However, these positive outcomes were accompanied by an increased incidence of high-grade immune-related toxicities, often necessitating temporary treatment discontinuation or the initiation of immunosuppressive therapy [61].

A meta-analysis further confirmed that obesity may serve as a favorable prognostic factor for response to immunotherapy in solid tumors, while also highlighting a heightened risk of specific adverse events, such as severe immune-related hepatotoxicity and gastrointestinal complications [55]. These findings underscore the necessity for close monitoring and individualized treatment planning in obese patients undergoing checkpoint inhibitor therapy.

At the same time, emerging research suggests potential benefits from adjunctive agents such as metformin in obese patients with NSCLC. Smith et al. [62] reported that combining immunotherapy with metformin was associated with a statistically significant improvement in response duration and overall survival compared to immunotherapy alone (median survival of 22 months vs. 15 months, $p < 0.01$). This benefit is thought to stem from improved metabolic homeostasis, AMPK activation, and modulation of the tumor microenvironment, thereby enhancing anti–PD-1/PD-L1 responses.

In summary, the impact of obesity on immunotherapy outcomes in lung cancer is multifaceted and context-dependent. While obesity may augment the effectiveness of immune checkpoint blockade and be associated with better survival metrics in selected cohorts, it also confers an elevated risk of immune-related adverse effects, requiring vigilant monitoring and possible therapeutic adjustments. These findings advocate for a personalized

approach to managing obese patients receiving immunotherapy – one that incorporates not only BMI but also body composition, metabolic status, immune markers, and potential adjunctive strategies (e.g., metformin or lifestyle interventions) to optimize treatment efficacy and minimize toxicity.

6. Impact of Obesity on Targeted Therapy in Lung Cancer

Targeted therapy is a crucial component of modern treatment for patients with NSCLC, particularly in the presence of molecularly defined driver mutations such as EGFR mutations or ALK rearrangements. These therapies, including EGFR tyrosine kinase inhibitors (TKIs) and ALK inhibitors, selectively block signaling pathways that drive tumor cell proliferation, resulting in effective inhibition of tumor growth and improved survival. However, obesity and its associated metabolic alterations can substantially influence the efficacy of these agents by modulating both molecular resistance mechanisms and pharmacokinetic aspects of treatment.

One key molecular link between obesity and therapeutic response to EGFR-targeted therapy involves the fat mass and obesity-associated (FTO) gene. FTO encodes an enzyme that demethylates N^6-methyladenosine (m6A) in mRNA, thereby regulating the stability and expression of numerous genes. In a study by Rastogi et al. [63], increased FTO activity in NSCLC tissues was associated with enhanced tumorigenicity and the development of resistance to EGFR TKIs. Molecular analyses showed that FTO promotes demethylation of transcripts encoding critical oncogenic proteins, thus supporting tumor cell survival despite concurrent EGFR blockade. These findings are significant because obesity correlates with elevated FTO expression, which may partially explain the attenuated response to EGFR-targeted therapy observed in this patient population.

Supporting the role of metabolic pathways in therapeutic resistance, Polonio-Alcalá et al. [64] demonstrated that inhibitors of fatty acid synthesis, particularly AZ12756122, can reduce features of resistance to EGFR TKIs in EGFR-mutant NSCLC cell models. Similarly, the fatty acid synthase inhibitor G28 exhibited antitumor activity in models of EGFR TKI–resistant lung adenocarcinoma, independent of EGFR mutation status [65]. These studies highlight that metabolic pathways related to lipogenesis and fatty acid distribution may serve as actionable targets to overcome resistance mechanisms that arise in the context of obesity.

Mechanistically, fatty acid synthesis plays a pivotal role in tumor cell proliferation and survival. It has been shown that fatty acid synthesis facilitates palmitoylation of EGFR, a post-translational modification that stabilizes the receptor at the cell membrane and enhances its signaling activity. This modification may reduce the effectiveness of EGFR TKIs, as a palmitoylated receptor is less susceptible to competitive inhibition. These findings align with the concept that metabolic stress and increased activity of fatty acid synthesis pathways – common features of obesity – can contribute to reduced sensitivity to targeted therapies [66].

Beyond EGFR-directed therapy, obesity can also influence responses to other targeted agents, such as ALK inhibitors. Clinical observations have revealed that patients treated with ALK inhibitors (e.g., alectinib and lorlatinib) frequently experience significant weight gain during therapy, an effect that may reflect both drug-specific metabolic impacts and interactions with underlying adipose tissue biology. Studies by de Leeuw et al. (2023) and pooled analyses by Sikkema et al. (2025) have documented substantial increases in body weight among patients receiving alectinib, with some individuals experiencing gains exceeding 10% of baseline body mass. Such weight changes can alter drug pharmacokinetics, impact comorbid conditions, and complicate long-term management.

Additionally, research by Watson et al. (2025) indicated that early weight gain during treatment with lorlatinib predicts more pronounced overall increases in body weight throughout the course of therapy. These weight changes may indirectly affect targeted therapy outcomes by modulating circulating growth factors, insulin/IGF signaling, and chronic inflammation – all of which intersect with tumor cell biology and drug response pathways.

Taken together, the influence of obesity on targeted therapy outcomes in lung cancer is multidimensional, involving direct modulation of oncogenic signaling through metabolic enzymes such as FTO, alterations to post-translational modifications of key receptor tyrosine kinases, and systemic metabolic adaptations that impact drug behavior and host–tumor interactions. Understanding these mechanisms underscores the importance of incorporating metabolic profiling and individualized patient assessment (including body composition and adipose distribution) into treatment

planning. Such approaches may guide the development of combination strategies, such as pairing targeted agents with metabolic modulators, to enhance therapeutic efficacy and overcome resistance in obese patients with NSCLC.

On a clinical level, the relationship between body mass and the effectiveness of targeted therapy is complex and multifaceted. For example, Minami et al. [67] found that a low BMI in NSCLC patients treated with EGFR TKIs was an independent adverse prognostic factor, associated with shorter median survival and more rapid disease progression. This finding suggests that not only excess body weight but also its absence can have clinically meaningful consequences for response to targeted therapy, particularly in the context of metabolic vulnerability of the tumor and the overall physiological reserve of the patient.

However, obesity's influence on therapy extends beyond direct molecular mechanisms. Pharmacokinetic changes related to the distribution and metabolism of targeted agents are also important. For example, in patients with ALK-positive NSCLC receiving ALK inhibitors such as alectinib or lorlatinib, significant weight gain during treatment has been documented. In the study by de Leeuw et al. [68], patients treated with alectinib experienced considerable weight increases, likely reflecting a side effect of the drug itself or metabolic adaptations to prolonged ALK signaling inhibition. A pooled analysis of four prospective clinical trials confirmed that weight gain in patients receiving alectinib is common and can, in some cases, exceed 10% of baseline body weigh*t* [69]. Such changes can influence the distribution and bioavailability of targeted drugs, as well as coexisting comorbid conditions, all of which may collectively modulate both therapeutic efficacy and safety.

Similar phenomena have been observed with other ALK inhibitors. Watson et al. [70] found that early weight gain during lorlatinib therapy predicted a more pronounced overall increase in body weight throughout treatment, which may affect the patient's metabolic status. Changes in body weight and associated metabolic adaptations can indirectly influence the effectiveness of targeted therapy by modulating systemic factors such as insulin levels, insulin-like growth factor 1 (IGF-1), and inflammatory cytokines, which are known to interact with tumor signaling pathways and affect sensitivity to inhibitors.

Taken together, these data underscore that body composition and metabolic status may be as important as the tumor's molecular profile in predicting response to targeted therapy. Indeed, clinical observations indicate that patients with metabolic comorbidities such as obesity and insulin resistance exhibit heterogeneous responses to EGFR TKIs, and that multi-omic models of tumor microenvironment and metabolic pathway assessment may provide superior predictive power for therapeutic outcomes.

In light of the foregoing, the impact of obesity on targeted therapy in lung cancer represents a convergence of molecular, metabolic, and pharmacological mechanisms that together can modulate both efficacy and safety of treatment. The use of personalized approaches, including assessment of nutritional status, body composition, molecular biomarkers, and tumor genetic profiles, has the potential to optimize therapy selection and improve outcomes for patients with obesity receiving targeted agents.

7. Conclusions

Obesity, as a metabolic disorder with systemic immune and endocrine ramifications, plays a significant role in the pathogenesis, clinical course, and treatment of non-small cell lung cancer. Over the past decades, the prevalence of obesity has risen steadily, mirroring epidemiological trends in lung cancer incidence and mortality. This concurrence underscores the importance of investigating common pathophysiological mechanisms and clinical implications arising from the interaction of these two conditions.

This monograph has systematically analyzed contemporary literature describing the influence of obesity on carcinogenesis, particularly through chronic inflammation, adipokine imbalance, metabolic remodeling of the tumor microenvironment, and immune dysregulation. Special attention was given to the impact of obesity on the effectiveness and tolerability of primary treatment modalities in lung cancer, including surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy. The evidence indicates that obesity can both worsen disease progression and, in select contexts, be associated with better therapeutic outcomes, giving rise to the phenomenon known as the obesity paradox.

Recognizing obesity as a biomedical and oncological modifier is crucial for personalized treatment planning in lung cancer. It should inform comprehensive supportive strategies aimed at improving not only oncologic outcomes but also overall metabolic health.

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