Review

Cutting-Edge Therapies for Lung Cancer

Anita Silas La'ah and Shih-Hwa Chiou *

Posted Date: 24 January 2024

doi: 10.20944/preprints202401.1751.v1

Keywords: lung cancer; conventional treatment; innovative therapeutic modalities; combination therapy

Review

Cutting-Edge Therapies for Lung Cancer

Anita Silas La'ah [1,2] and Shih-Hwa Chiou [1,3,*]

[1] Department of Medical Research, Taipei Veterans General Hospital, Taipei 112, Taiwan
[2] Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taipei 115, Taiwan
[3] Institute of Pharmacology, School of Medicine, National Yang Ming Chiao Tung University, Taipei 112, Taiwan
* Correspondence: shchiou@vghtpe.gov.tw

Abstract: Lung cancer remains a formidable global health challenge that necessitates inventive strategies to improve therapeutic outcomes. Conventional treatments, including surgery, chemotherapy, and radiation, have demonstrated limitations in achieving sustained responses. Therefore, the exploration of novel approaches encompasses a range of interventions that show promise in enhancing outcomes for patients with lung cancer, particularly those facing advanced or refractory cases. These groundbreaking interventions hold the potential to overcome cancer resistance and offer personalized solutions. Despite the rapid evolution of emerging lung cancer therapies, persistent challenges such as resistance, toxicity, and patient selection underscore the need for continued development. Consequently, the landscape of lung cancer therapy is transforming with the introduction of precision medicine, immunotherapy, and innovative therapeutic modalities. Additionally, a multifaceted approach involving combination therapies through the integration of targeted agents, immunotherapies, or traditional cytotoxic treatments addresses the heterogeneity of lung cancer while minimizing adverse effects. This review provides a brief overview of the latest emerging therapies that are reshaping the landscape of lung cancer treatment. As these novel treatments progress through clinical trials and integrate into standard care, the potential for more effective, targeted, and personalized lung cancer therapies comes into focus, instilling renewed hope for patients facing challenging diagnoses.

Keywords: lung cancer; conventional treatment; innovative therapeutic modalities; combination therapy

1. Introduction

Lung cancer remains the primary cause of cancer-related deaths worldwide despite the progress made in cancer diagnosis and emerging treatment methods [1]. The 5-year overall survival rate for lung cancer patients is 19% across all stages of the disease. However, as the disease progresses from early to advanced stages, there is a significant decline in the 5-year survival rate [2]. This is also observed in lung cancer patients with stage 1 tumors, where the 5-year recurrence-free survival only slightly exceeds 80% following curative surgical resection [1]. This implies that approximately 20% of individuals with lung cancer undergo disease recurrence within five years, underscoring the lack of a conclusive cure. Furthermore, a significant portion of lung cancer patients, constituting 57%, are diagnosed with metastasis, and their survival rate is as low as 5% [3].

Innovative approaches are continually shaping the landscape of lung cancer treatment, offering improved outcomes and novel options for patients. Advancements in this field encompass immunotherapy, targeted therapy, cryoablation, and the utilization of nanoparticle-based drug delivery systems, along with the evolving realm of gene therapy. However, ongoing research holds the promise of additional breakthroughs, contributing significantly to successful clinical outcomes that may revolutionize the care of lung cancer patients [4-6]. Combinatorial therapeutic approaches represent a significant spectrum of innovative strategies. The ESMO Congress 2023 notably highlights the efficacy of combining targeted drugs and immunotherapy, especially for lung cancer patients with EGFR mutations and rare tumor alterations. These advancements are poised to play a

 doi:10.20944/preprints202401.1751.v1

substantial role in revolutionizing the landscape of lung cancer treatment. In this review, we present a concise summary of such innovative therapeutic approaches.

2. Targeted Therapies

Molecular alterations such as EGFR mutations, ALK rearrangements, ROS1 rearrangements, RET rearrangements, NTRK fusions, MET exon 14 skipping mutation, KRAS G12C mutation, BRAF V600E mutation, and ERBB2 (HER2) mutations are the major factors underlying the aggressiveness of lung cancer. Therefore, targeted therapies are designed to overcome the consequences of these mutations and largely achieve great success in the treatment and prognosis of this formidable disease, resulting in an improved survival rate [7]. Despite the emergence of such therapies, the significant challenge remains as many oncogenic driver mutations still lack specific targeted agents, and resistance is a recurring issue.

2.1. Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal growth factor receptor (EGFR) activating mutations are prevalent in non-small cell lung carcinoma (NSCLC), the most common type of lung cancer, with exon 19 deletions and L858R point mutation being the most frequent alterations. The discovery of tyrosine kinase inhibitors (TKIs) designed to target EGFR mutations in lung cancer patients marked the inception of the precision medicine era in lung cancer. EGFR-TKIs have been designed to target these mutations effectively by inhibiting the activation of tyrosine kinase domain and disrupting various EGFR-dependent/independent downstream signaling pathways in the lung [8]. Currently, there are three generations of clinically available EGFR-TKIs, namely: the first generation of reversible inhibitors (gefitinib, erlotinib, and icotinib), the second generation of irreversible inhibitors (afatinib, dacomitinib), and the third generation of irreversible inhibitors (osimertinib, almonertinib, lazertinib) [8]. Whereas the first and second generation TKIs can effectively inhibit EGFR with exon 19 deletions and L858R mutation, the resistance invariably arises mainly due to T190M mutation [9] [10]. To overcome this major challenge, a clinical trial (NCT02296125) has explored the effectiveness of osimertinib, a third-generation TKI, in treating untreated advanced NSCLC with EGFR mutations. The study demonstrated a significant impact with fewer adverse effects on NSCLC patients compared to standard EGFR-TKIs used in the initial treatment [11]. Simultaneously, BBT-176 is under development as a fourth-generation EGFR TKI, demonstrating significant potency against the C797S mutation that confers resistance to third-generation TKIs [12].

Monoclonal antibodies offer an alternative strategy for inhibiting EGFR activation and signaling. These antibodies not merely form complexes with the receptor that are internalized and eliminated but can also entirely block ligands from attaching to the extracellular domain. Available monoclonal antibodies targeting EGFR include cetuximab, necitumumab, panitumumab, and matuzumab. In two phase III trials, FLEX and BMS099, a combination of cetuximab and platinum doublet chemotherapy was employed to treat advanced NSCLC [13, 14]. Additionally, amivantamab, a bispecific antibody targeting both EGFR and MET, was used to treat NSCLC specifically associated with EGFR exon 20 insertions [15]. In a preclinical study, the combination of amivantamab and lazertinib, which targets both the EGFR extracellular and catalytic domains, demonstrated synergistic tumor growth inhibition [16].

EGFR-TKIs significantly enhance the objective response rate, progression-free survival, and quality of life when compared to conventional chemotherapeutic approaches, all while presenting minimal toxicity [17, 18]. The adoption of EGFR-TKIs marks a significant leap forward in the treatment of NSCLC, ushering in an era of targeted therapy and precision medication.

2.2. Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) Inhibitors

Kirsten rat sarcoma viral oncogene homolog (KRAS) is a well-known oncogene encoding Ras family small GTPase controlling crucial proliferation and survival pathways. Among three members of the Ras family, KRAS is the most frequently mutated in cancers (85%), followed by NRAS (11%)

 doi:10.20944/preprints202401.1751.v1

and HRAS (4%). The most frequent KRAS activating mutations occur at amino acid positions G12, G13, and Q61 [19]. Ras oncogenes play a crucial role in oncogenesis and, therefore, have been naturally considered as potent targets for cancer therapy. However, several efforts to target Ras proteins have faced considerable challenges due to molecular features such as highly dynamic structure and high intrinsic flexibility precluding stable binding of the inhibitors, thus making them to be deemed "undruggable" [20]. However, new technologies and insights into KRAS signaling pathways have renewed efforts to develop therapies for KRAS-driven cancers. These include direct targeting of KRAS or indirect targeting by blocking upstream factors activating KRAS [21].

A direct approach to targeting KRAS in lung cancer involves using sotorasib (AMG510) and adagrasib (MRTX849). Sotorasib is a covalent inhibitor designed for KRAS G12C and marked a milestone as the first KRAS inhibitor to receive US Food and Drug Administration (FDA) approval on May 28, 2021 [22]. This drug covalently binds to the mutant cysteine 12 in the switch II region, prompting KRAS to stay in inactive GDP-bound form. Consequently, it inhibits KRAS signaling and suppresses the MAPK pathway. In a phase II clinical trial encompassing 126 patients with advanced NSCLC, sotorasib demonstrated a 37.1% response rate, a progression-free survival of 6.8 months, and a median overall survival of 12.5 months [23]. Adagrasib is another FDA-approved small molecule directly targeting KRAS G12C by covalent binding to the mutant cysteine 12, effectively inhibiting KRAS-dependent signaling, such as MAPK pathway [19]. Clinical trials actively explore the potential of other drugs that covalently inhibit KRAS G12C, such as divarasib (GDC-6036) from Genentech, which is currently undergoing a phase 1 clinical trial (NCT04449874) as a monotherapy and combined with other anticancer therapies. This research is being conducted on patients with advanced/metastatic solid tumors carrying a KRAS G12C mutation [20].

Another chemotherapeutic approach is to target KRAS indirectly by inhibiting its upstream regulators. Currently, a phase I clinical trial (NCT04111458) is evaluating the efficacy of BI1701963, an inhibitor of SOS1, which serves as a guanine nucleotide exchange factor turning KRAS into its GTP-bound active form. This study investigates the effectiveness of BI1701963 both as a monotherapy and in combination with the MEK inhibitor trametinib [24]. Additionally, Novartis Pharmaceuticals is conducting a phase I/II clinical trial (NCT04699188) to assess the effectiveness of TNO155, an inhibitor of tyrosine phosphatase SHP2, which serves as another upstream factor responsible for KRAS activation. It is being tested as both monotherapy and in combination with spartalizumab anti-PD1 antibody immunotherapy in patients with advanced or metastatic solid tumors featuring the KRAS G12C mutation [20]. Jacobio Pharma is also actively investigating the efficacy of JAB-21822, the inhibitor of KRAS G12C, in various clinical trials, either as a monotherapy or in combination with JAB-3312 SHP2 inhibitor or cetuximab anti-EGFR immunotherapy [25].

To summarize, direct targeting of KRAS has been challenging due to its high affinity for GTP at the picomolar level, the absence of appropriate pockets for high-affinity small-molecule binding, and elevated mutation rate. However, the covalent modification of mutated cysteine 12 in KRAS G12C proved to be a viable option. Despite this, cancer cells still develop resistance to these inhibitors, prompting the exploration of combination therapies and new approaches to treat KRAS-driven cancers.

2.3. Anaplastic Lymphoma Kinase (ALK) Inhibitors

The anaplastic lymphoma kinase (ALK) receptor tyrosine kinase plays a pivotal role in cellular development, and alterations in the ALK gene may occur in cancers such as anaplastic large cell lymphoma, neuroblastoma, and NSCLC. When the ALK gene is activated in cancer, it can lead to cell development and rapid growth. This activation of ALK signaling in tumor cells is brought about by mechanisms such as gene fusions, chromosomal translocations, gene amplification or deregulation, and activating point mutations [26, 27]. In the treatment of NSCLC patients with ALK alterations, there are targeted inhibitors such as crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib, which offer significant benefits [28]. Crizotinib is a potent small-molecule drug that effectively targets the tyrosine kinases ALK and c-MET [29]. Clinical studies in phase I/II have demonstrated that crizotinib enhances progression-free survival in combination with bevacizumab, the angiogenesis-inhibiting

 doi:10.20944/preprints202401.1751.v1

antibody [30]. On the other hand, ceritinib, a second-generation ALK inhibitor, has been utilized to treat advanced or metastatic ALK-positive NSCLC, even in patients resistant to crizotinib [31, 32]. Despite the initial effectiveness of existing ALK inhibitors, resistance inevitably develops. SAF-189s is a novel ALK inhibitor that has shown promise in overcoming the majority of known resistance mutations associated with ALK in preclinical studies and is currently undergoing a phase I/II study in China [33]. APG-2449 is a triple kinase inhibitor of ALK, ROS1, and FAK that has shown anti-tumor activity in a mouse model of ALK/ROS1-positive NSCLC. Currently, it is undergoing evaluation in a phase I dose escalation and expansion trial (NCT03917043), which enrolled 84 patients diagnosed with ALK/ROS1-positive NSCLC [34].

2.4. ROS Proto-oncogene 1 Receptor Tyrosine Kinase (ROS1) Inhibitors

ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) is a paralog of ALK belonging to the insulin receptor family that functions as a growth or differentiation factor receptor. The incidence of ROS1 rearrangements is observed in 1% to 2% of NSCLC cases. Although some ROS1 inhibitors, specifically crizotinib (first generation), entrectinib (second generation) and lorlatinib (third generation), have received FDA approval for treating ROS1-positive NSCLC, the majority of patients still encounter challenges with treatment resistance and disease progression [18, 35]. Clinical investigations have evaluated the effectiveness of additional inhibitors in patients with ROS1-positive NSCLC, including repotrectinib [36] and taletrectinib [37]. Both of these inhibitors received FDA approval in 2022 [7].

3. Immunotherapy

Immunotherapy has markedly reshaped the treatment of cancer, owing to its well-tolerated safety profile, capacity to induce enduring therapeutic responses through the generation of immunological memory, and effectiveness across a broad spectrum of patients [38]. There are various emerging methods in lung cancer immunotherapy, including tumor-specific vaccination strategies, immune checkpoint inhibitors, adoptive cell therapy, etc. [39]. Several clinical trials have been conducted to assess the efficacy of immunotherapy in lung cancer, specifically in patients facing challenges that involve the absence of a targetable driver mutation [5]. Cancer immunotherapies are carried out mainly to impede tumor growth and enhance the survival outcomes of patients by boosting the host's anti-tumor immunity and modifying the suppressive tumor microenvironment [40].

3.1. Adoptive Cell Transfer

Adoptive Cell Transfer (ACT) for lung cancer involves extracting T cells from the patient's bloodstream [41]. An example of adoptive cell transfer is CAR-T cell therapy, which involves the genetic modification of T lymphocytes from lung cancer patients to make them express chimeric antigen receptors (CARs) [42]. Such CAR-T is introduced back to the body, and the CARs recognize the antigens expressed by cancer cells, which trigger their destruction [43]. Furthermore, tumor-infiltrating lymphocytes (TILs) represent another type of adoptive cell transfer application that entails isolating TILs from the tumor site through biopsy or surgery. Subsequently, these isolated TILs are stimulated with interleukin-2 (IL-2) and reintroduced into the patient through infusion, with the aim of targeting and attacking the cancer cells [44].

3.2. Immune Checkpoint Inhibitors

Checkpoint proteins such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) constitute a restraining mechanism of the immunity system that prevents it from autoimmune reactions but at the same time associated with immune escape by cancer cells. However, dysregulation in these pathways is associated with immune escape with an increase in cancer progression [45]. Immune checkpoint inhibitors have shown inspiring clinical efficacy and safety in treating lung cancer. Several clinical

 doi:10.20944/preprints202401.1751.v1

trials have been conducted to investigate the effectiveness of these inhibitors, aiming to enhance overall survival and progression-free survival in NSCLC patients. For instance, pembrolizumab (Keytruda) and nivolumab (Opdivo), antibodies designed against PD-1 and CTLA-4, both have demonstrated effectiveness in lung cancer treatment [46].

3.3. Cancer Vaccines

DNA and mRNA vaccines for cancer have become a promising strategy for both prevention and treatment. This method includes the introduction of DNA or RNA sequences that encode tumor-associated antigens (TAAs) or neoantigens, resulting in specific targeting of cancer cells [47]. Despite being in the early stages of development and clinical testing, therapeutic cancer vaccines, particularly for lung cancer, show potential in treating patients resistant to standard-of-care treatment [48].

3.4. Oncolytic Viruses (OVs)

In the treatment of lung cancer, oncolytic viruses (OVs) operate by selectively identifying, infecting, and eliminating cancer cells while minimizing harm to healthy cells [49]. The main mechanism of OVs involves inducing specific antitumor immune responses and selective cell death, resulting in tumor cell lysis and a reduction in tumor progression [50]. This immune response contributes to long-term cancer control and prevention of cancer recurrence. An example of an OV is reovirus, which can be engineered for targeted cancer cell treatment or may naturally exhibit a preference for infecting cancer cells. Reovirus can be employed either independently or in combination with other therapies like chemotherapy, radiotherapy, or gene therapy [51]. The combination of OVs with other lung cancer treatments holds the potential to enhance effectiveness and improve overall patient outcomes [52].

4. Radiation Therapy

Radiotherapy is a conventional method employed in the treatment of lung cancer; however, a notable challenge lies in the deposition of doses on healthy tissues before reaching the intended targets, and this is likely to cause severe complications in patients with recurrent cancer. This necessitates the development of more targeted approaches allowing the specific destruction of cancer while sparing healthy tissues. Some promising approaches in radiation therapy are listed below.

4.1. Boron Neutron Capture Therapy (BNCT)

Boron neutron capture therapy (BNCT) is an emerging treatment method in radiation therapy that selectively targets and eliminates cancer cells while sparing normal cells [53]. This method is based on a preferential accumulation of compounds containing boron isotope ^{10}B in cancer cells. Upon exposure to a beam of low-energy neutrons, ^{10}B converts into unsTable $1^{1}B$, which decays into α particles (^{4}He) and ^{7}Li recoil particles. The high-energy particles generated through boron-neutron interaction exhibit a limited impact range, primarily affecting the cells where boron is concentrated. This leads to localized damage to cancer cells, sparing the surrounding healthy tissues [53].

Metastatic lung disease remains a predominant cause of mortality despite the limited success of surgery, radiotherapy, and chemotherapy in enhancing patient survival. In this context, BNCT is a pivotal treatment option known for its selectivity and lower toxicity. As was shown in the BDIX rat model with lung metastases of colon carcinoma, BNCT showed no toxicity and suppressed lung metastases at a short treatment time [54, 55]. In an animal model of metastatic clear cell sarcoma (CCS), BNCT markedly diminished the growth of lung metastases associated with CCS tumors [56]. Previous mouse model studies have suggested that BNCT can be used to treat both lung tumors and lung metastases tumors [57]. BNCT mediated by ^{10}B-carrier L-para-boronophenylalanine-^{10}B (BPA) treatment was also monitored in the normal lung of Fischer 344 rats by assessing the established relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors [58]. This method was employed in patients with recurrent lung cancer who had previously undergone chest wall irradiation with two fractions of BNCT. The tumor exhibited regression within seven months,

 doi:10.20944/preprints202401.1751.v1

with minimal or delayed adverse effects [59]. As was shown in a mouse model, the combination of BPA-mediated BNCT with both mild temperature hyperthermia and hypoxic cytotoxin tirapazamine (TPZ) targeting quiescent tumor cell population significantly reduced lung metastases [60]. Apart from the distribution of 10B concentration, neutron sources characterized by different energy spectra are also an important consideration for successful BNCT.

For instance, dose distribution based on different neutron sources has recently been optimized to treat shallow or deeper lung tumors [61]. A similar dose distribution analysis was performed to optimize the BNCT treatment of mesothelioma [62]. To summarize, BNCT is a recognized strategy that proved to be an effective means of enhancing the survival rates for lung cancer patients and those with metastatic lung tumors, leading to improved patient outcomes.

4.2. Proton Therapy

Proton therapy is an advanced cancer treatment that employs proton beams to eliminate tumors by delivering precise and accurate doses, minimizing harm to surrounding healthy tissues [63]. In NSCLC, proton therapy shows promise as a treatment modality due to its utilization of the Bragg peak as a physical property, where most of the proton dose is concentrated within a narrow range, minimizing the impact on normal thoracic tissues [64]. In cases of centrally or superiorly located stage I NSCLC, intensity-modulated proton therapy (IMPT) doses can precisely be administered to the target area, resulting in a substantial decrease in radiation exposure to normal tissues such as the heart, aorta, pulmonary vessels, lung, brachial plexus, and spinal cord when compared to photon stereotactic body radiation therapy [65].

Several clinical trials were conducted; for example, the RTOG 1308 trial (NCT01993810) is a phase III randomized trial that employed the treatment of non-operable stage II–IIIB NSCLC patients with a total dose of 70 Gy (2 Gy per fraction) alongside concurrent chemotherapy, utilizing image-guided, motion-managed proton or photon radiation techniques. This trial has demonstrated cost-effective access to pulmonary function assessments before and after radiation treatment, resulting in improved survival outcomes [66]. LUN005 (NCT0177041) is a combined phase I/II clinical trial undertaken on stage II/III NSCLC patients to examine the viability after hypofractionated proton therapy administered concurrently with chemotherapy. The phase I trial aimed to establish the maximum tolerated dose per fraction, reaching a cumulative total of 60 Gy. Subsequently, the phase II trial assessed outcomes such as survival at 12 months, adverse events, and tumor control [67]. In conclusion, proton therapy offers a targeted and potentially less harmful method for addressing lung cancer, especially when the preservation of adjacent healthy tissues is paramount. Nevertheless, the accessibility and broader integration of this treatment approach are still at a stage of exploration and development.

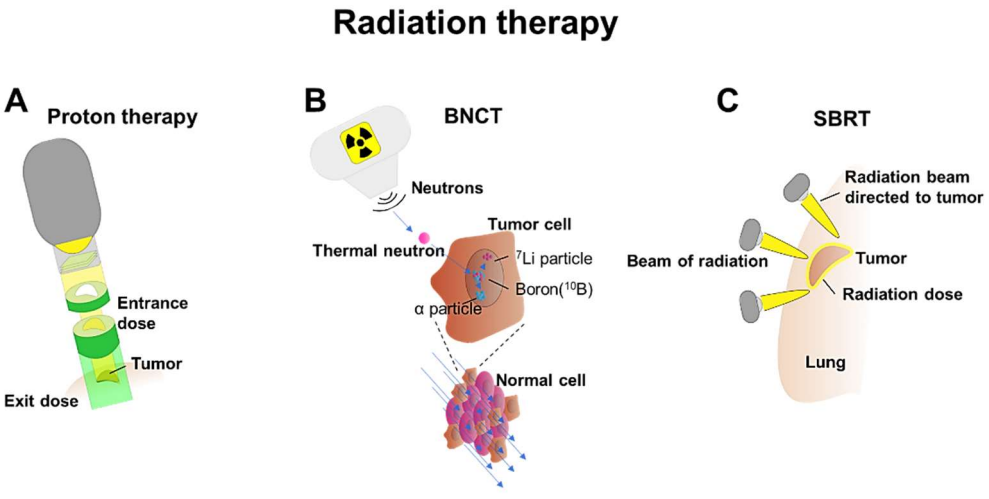

Figure 1. Emerging radiotherapy strategies: **(a)** Proton therapy: Proton beam radiation targets the tumor and spares healthy tissue by moving safely within the body and releasing energy that destroys

 doi:10.20944/preprints202401.1751.v1

cancer cells; **(b)** BNCT: After administration of a non-radioactive compound containing the inert isotope 10B, which specifically homes in cancer cells, the patient is exposed to a low-energy neutron beam. This beam initiates the fission of the ^{10}B isotope within the tumor cells, leading to the emission of a high-energy α-particle. This particle selectively kills cancer cells containing^{10}B isotope compound; **(c)** SBRT: A 4-dimensional CT scan is employed to observe the movement of lung cancer during inhalation and exhalation. High-dose radiation beams from various angles are then precisely directed at the tumor.

4.3. Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) is an efficient and potentially effective option for treating NSCLC patients that are inoperable. It is a noninvasive treatment that delivers high doses of radiation with precision in a few treatments, achieving superior local control and survival rates compared to conventional radiation therapy [68]. SBRT utilizes sophisticated imaging and localization techniques to enhance the precision of radiotherapy targeting. This optimization enables the administration of hypofractionated and ablative doses of radiation [69]. The effectiveness of SBRT lies in its ability to deliver therapeutic radiation doses with a relatively high probability of tumor control while minimizing the exposure of normal tissue to these doses [70]. For instance, patients diagnosed with lung cancer, regardless of whether they had undergone prior lung resection or not, received SBRT demonstrated high local control and relatively low toxicity [71].

SBRT has been employed in 19 prospective clinical trials for primary early-stage NSCLC, encompassing 1434 patients with central and peripheral early-stage NSCLC. The findings revealed that SBRT demonstrated excellent local and regional control, with survival rates ranging from 43% to 95% at three years. Nevertheless, up to 33% of patients experienced distant failure following SBRT. The treatment was generally well-tolerated, with 10%-30% of patients encountering grade 3-4 toxicities and a limited number of treatment-related deaths. No discernible differences in outcomes were noted between conventional fractionated radiation therapy and SBRT or among central and peripheral lung tumors, as well as between inoperable and operable patients [72].

SBRT is gaining prominence in intricate cases, including patients with tumors situated close to vital organs, those with a history of previous radiation exposure, individuals with interstitial lung disease (ILD), or patients with metastatic disease. Among patients with ILD, SBRT poses an elevated risk of toxicity; nevertheless, it remains the standard care for non-operable NSCLC patients. In instances of ultracentral tumors (those close to the trachea or proximal bronchial tree), SBRT poses an increased risk of severe toxicity, encompassing pulmonary hemorrhage or airway necrosis [68]. SBRT remains a viable treatment choice for medically inoperable and operable patients diagnosed with early-stage NSCLC, providing excellent local and regional control, accompanied by lower toxicity rates [73].

4.4. Brachytherapy (BT)

Brachytherapy (BT) emerged as a promising radiotherapy choice for lung cancer, enhancing local control and extending patient survival outcomes. This minimally invasive radiotherapeutic method involves the precise implantation of a radioactive source directly within or close to the tumor, thus delivering targeted irradiation [74]. BT is valuable as a salvage treatment for specific patients experiencing local recurrence or residual lung cancer following a lack of response to interventions, such as surgery, chemotherapy, and external beam radiation therapy (EBRT) [75, 76].

In lung cancer, BT can be administered through endobronchial BT and radioactive seed implantation [75]. BT is recognized as an effective treatment for lung cancer patients. An earlier study detailed the case of a 79-year-old patient diagnosed with early-stage NSCLC with no surgical intervention or SBRT due to the radiologically occult characteristics of the tumor. Instead, the patient underwent treatment with high-dose-rate endobronchial BT (HDR-EBBT), receiving four weekly sessions with a dosage of 7 Gy per fraction. Over time, a new lung cancer developed, prompting treatment with SBRT; however, the latest computerized tomography (CT) scan revealed no detectable signs of disease [77]. Additionally, a clinical study involving 23 patients treated with HDR-EBBT,

 doi:10.20944/preprints202401.1751.v1

whether for curative or palliative purposes, indicated that HDR-EBBT is more efficacious in achieving local control in both curative and palliative scenarios, leading to an enhanced overall survival rate [78]. Another study also proposed that HDR-EBT is a secure technique for the comprehensive treatment of endobronchial lung cancer. The study involved 16 predominantly male patients with an average age of 69 years, most of whom were former smokers. The primary pathological diagnosis was invasive squamous cell carcinoma, and the treatment protocol included the insertion of an after-loading catheter into the target bronchus, followed by weekly HDR-EBT sessions. The median overall survival was 29 months, accompanied by a median disease-free survival of approximately 24.9 months. Two complications were observed but without any death or significant side effects. Notably, patients who underwent a boost strategy with HDR-EBT exhibited a prolonged overall survival compared to those undergoing radical intent treatment [79]. To improve the efficacy of BT in lung cancer, a multicenter randomized trial was conducted to enhance the effectiveness of BT by combining high-dose-rate intraluminal BT (HDRIB) with external beam radiation therapy (EBRT). The trial revealed moderate symptom relief without achieving statistical significance [80]. Endobronchial BT and radioactive seed implantation BT (RSI-BT) are viable methods for BT in lung cancer.

5. Cryoablation

Cryoablation is a therapeutic approach whereby tumors are destroyed by extreme cold [81]. This process involves connecting cryoprobes to pressurized argon, which rapidly cools the probe upon its expansion to temperatures as low as -160°C. Consequently, this results in the formation of an ice ball at the tip of the cryoprobe. The freezing and thawing process disrupts the cell membrane and initiates microvascular injury, subsequently inducing hypotonic stress and leading to cell necrosis [82]. In lung tumors, cryoablation is typically conducted with the guidance of CT scans, accompanied by sedation and local anesthesia [81]. The procedure can be performed through endobronchial, direct intrathoracic, or percutaneous routes, depending on the location and size of the tumor [83]. Some adverse effects faced by lung cancer patients include mild complications such as bleeding, pneumothorax, and pulmonary infection [81].

Typically, patients with lung metastases frequently struggle to attain curative results despite undergoing chemotherapy, radiotherapy, or surgery [82]. However, studies indicate that cryoablation can potentially treat lung metastasis effectively [84]. A promising strategy involves combining cryoablation with immunotherapy; however, cryosurgery alone cannot elicit a robust immunotherapeutic response against cancer [82]. The administration methods for combining cryoablation with immunotherapy include percutaneous and bronchoscopic approaches [83]. Clinical trials were carried out to explore the effectiveness of combining cryosurgery with allogeneic NK cell immunotherapy for treating NSCLC. The research revealed improved immune function in patients, which led to significantly higher response rates and disease control rates when compared to the cryoablation-only group [85]. Furthermore, in patients with advanced NSCLC, the therapeutic impact of cryoablation was elevated when combined with gefitinib [86]. Comparative studies on NSCLC indicated that both cryoablation and microwave ablation were safe and effective for small tumors. Nevertheless, microwave ablation demonstrated a superior effect when dealing with larger tumors [87]. These recent extended follow-up studies suggest that cryoablation is emerging as a notable choice for diverse cancers, providing the prospect of prolonged survival.

6. Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a non-invasive treatment of lung cancer that utilizes photosensitive compounds and light activation to destroy cancer cells selectively [65]. PDT has demonstrated efficacy in enhancing the survival rate of patients with incurable malignancies by using three fundamental factors: photosensitizer drug, light, and oxygen [88]. Photosensitizers exert their photodynamic activity through photo-oxidative mechanisms, triggering diverse biochemical and morphological reactions that lead to cytotoxic effects in tumors [89]. For instance, chlorin e6 (Ce6) is a frequently used photosensitizer that causes DNA damage and elicits a DNA damage response

 doi:10.20944/preprints202401.1751.v1

(DDR) in lung cancer cells. When such PDT treatment is combined with the inhibition of ATM serine/threonine kinase responsible for DDR, lung cancer cells are effectively destroyed [90]. However, the effectiveness of PDT is largely constrained by the lipophilic nature of photosensitizers and limited tissue infiltration [91]. The applicability of PDT tends to be limited to superficially located tumors that can be easily accessed by a bronchoscope with a light source [92]. For instance, it can be used as a complementary measure to treating advanced stage lung cancers in which the tumors have spread to the bronchoscope-accessible areas. In such cases, it is typically employed alongside chemotherapy and radiation rather than as a replacement [93].

The integration of nanotechnology into PDT has the potential to surmount its limitations by facilitating drug delivery and release [94]. This can result in more efficient and precisely targeted treatment approaches for lung cancer [95]. For instance, Ce6-conjugated methoxy-poly (ethylene glycol)-b-poly (D, L-lactide) (mPEG-PLA-Ce6) amphiphilic polymer nanoparticles were utilized as a Ce6 carrier in PDT and elicited enhanced phototoxicity and efficient internalization in both monolayers and 3D spheroids of human lung adenocarcinoma cells [96]. In another study, mesenchymal stem cells (MSCs) characterized by high tumor-tropism were loaded with MnO2@Ce6 nanoparticles to specifically deliver photosensitizer to the lung cancer site and target it for PDT in a mouse model [97].

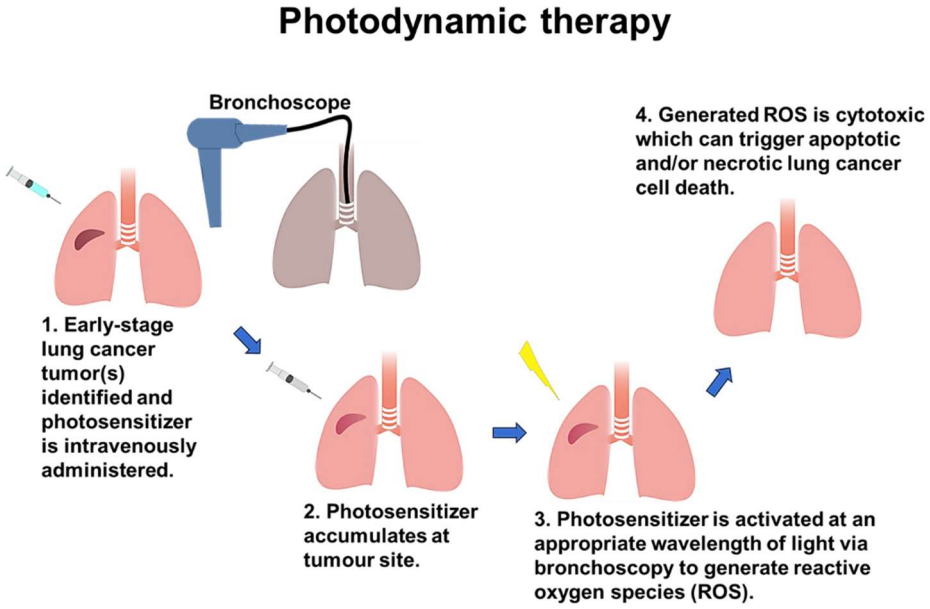

Figure 2. Simplified photodynamic therapy steps: (1) The patient receives a photosensitizer (PS) drug through injection near the tumor; (2) The PS drug gathers at the tumor site, either actively or passively; (3) After absorption by the tumor, laser light at the right wavelength (630 nm-780 nm) is used to activate the PS; (4) Activation results in targeted destruction of the tumor cells.

Several PDT clinical trials have been undertaken; the most recent significant study was centered on the combination of Laserphyrin®-based PDT and chemotherapy for advanced NSCLC cases in which curative surgical interventions were not feasible. The aim was to address bronchial stenosis and obstruction in central and peripheral (lobar or segmental bronchi) lung areas, and PDT resulted in improved symptoms and quality of life [98]. Additionally, second-generation Radachlorin®-based PDT was employed for advanced NSCLC, resulting in a one-year post-treatment survival rate of 70% with improved treatment effectiveness and safety [99]. A phase 1 clinical trial of PDT targeting carcinoma in situ and microinvasive carcinoma in the central airways was carried out with the use of 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH) as a photosensitizer. This approach demonstrated safety and efficacy in treating NSCLC by attaining a complete response (CR) rate of 72.7% at six months [100]. Furthermore, integrating high dose rates of BT and PDT for endobronchial tumors at different stages (I–IV) has proven to be well tolerated. This combined approach allowed to

 doi:10.20944/preprints202401.1751.v1

achieve prolonged local control and maintain an acceptable level of morbidity [101]. A novel PDT technique, intelligent targeted antibody phototherapy (iTAP), has recently been proposed. This method is based on the combination of cetuximab immunotoxin treatment and mono-L-aspartyl Pe6 (NPe6)-based PDT and was shown to be a minimally invasive yet highly effective treatment compared to conventional PDT [102].

7. Hyperthermia Therapy

Hyperthermia therapy (HT), or thermal therapy, is a cancer treatment involving the artificial elevation of body tissue temperature. This is accomplished by administering heat from external sources such as microwaves, radio waves, lasers, ultrasound, etc., to locally elevate temperature to 42 - 45°C. This process aims to eliminate cancer cells or inhibit their growth without causing harm to normal tissues [103]. HT induces direct cytotoxic effects on lung cancer cells [104], as well as enhances tumor perfusion, thus increasing drug delivery capability [105]. At temperatures above 42°C, tumor blood vessels can collapse, trapping the applied heat and leading to necrosis or apoptosis [106]. For example, HT was shown to trigger apoptosis of lung cancer cells mediated by caspase-3 and induced by the activation of cell death membrane receptors from the tumor necrosis family [107]. In another study, it was shown that HT and glutathione facilitate the release of doxorubicin from a mesoporous silica nanocontainer drug carrier in lung cancer cells, ultimately leading to cell death [108]. Additionally, the combination of cisplatin, cyclophosphamide, and HT in mice with metastatic Lewis lung carcinoma demonstrated a thermal potentiation of the growth delay induced by the combined drugs [109].

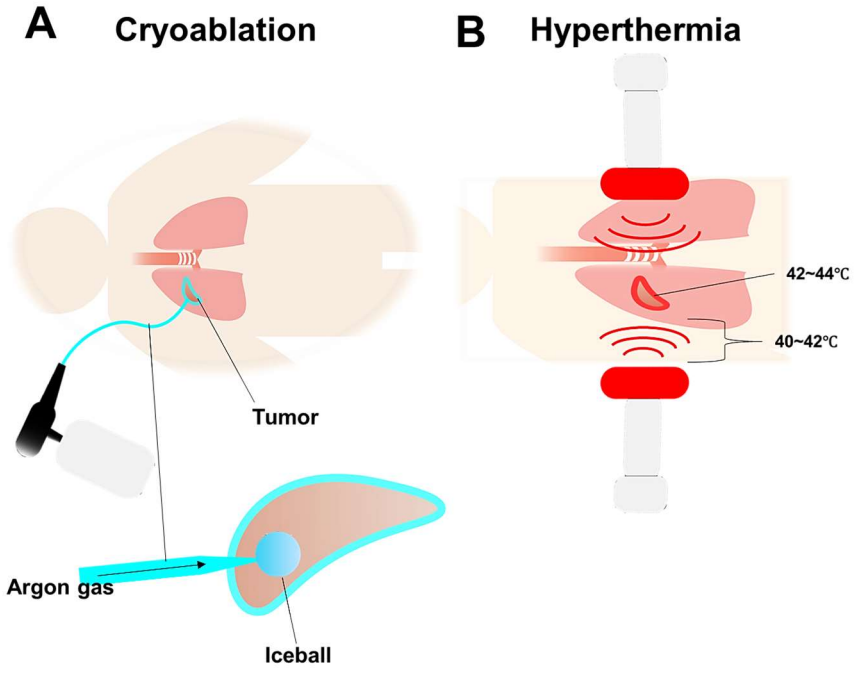

Figure 3. Simplified illustration showing how cryoablation and hyperthermia are carried out: **(a)** Cryoablation: During cryoablation, cryoprobe forms ice balls and delivers an extremely cold freezing agent to the tumor site. A CT scan is employed to visualize the tumor and guide the precise placement of the ice ball around the targeted tumor. After treatment, a warmed cryoprobe is safely extracted from the patient; **(b)** Hyperthermia involves heating body tissue up to 44°C to damage and eliminate cancer cells while minimizing harm to normal tissue. Small probes equipped with thermometers are inserted around the tumor to monitor and regulate temperature closely. CT scans and other imaging techniques ensure proper probe placement.

On the contrary, the temperature below 42°C influences the tumor microenvironment and increases blood flow and vascular permeability, thus potentially improving the supply of oxygen and

 doi:10.20944/preprints202401.1751.v1

nutrients to tumor cells. This makes precise temperature control a strict consideration for achieving the desirable effect of HT. For instance, the increase in perfusion acts as a coolant that dissipates the applied heat unless countermeasures are implemented [110]. Another limitation of HT is that it can induce coagulation, particularly with perfusion or whole-body HT techniques, which may lead to hypoxia and contribute to tumor radioresistance [110].

HT serves as a supplementary or adjunctive therapy when used in conjunction with radiation and chemotherapy, particularly in the case of inoperable lung cancer [111]. Consistently with the chemosensitization effect of HT, previous reports indicate that combining chemotherapy with HT has the potential to enhance the outcome in NSCLC with malignant pleural effusion [105]. The prominent challenge associated with radiotherapy is the deposition of toxins in healthy tissues [110]. HT can minimize this effect by acting as a radiosensitizer and thus allowing to lower dose of radiotherapy [112]. In another clinical study, re-irradiation combined with HT decreased the level of toxicity in recurrent NSCLC patients and increased long-term survival, particularly in cases without distant metastasis and those with larger recurrent tumors [113].

8. Nanoparticles as a Tool for Targeted Therapy

Nanomedicine represents an emerging treatment approach that emphasizes the enhancement of drug delivery and the optimization of therapeutic outcomes, with an aim to minimize harm to healthy tissues [114]. The biocompatibility and biodegradability of nanomaterials contribute to their effectiveness in drug-delivery systems [115]. Additionally, nanomaterials enhance the solubility, stability, and bioavailability of drugs, resulting in enhanced therapeutic efficacy [116]. Nanoparticles are also utilized to enhance cancer immunotherapy by boosting the immune response against cancer cells [117, 118]. Some nanomedicine materials, including hafnium oxide nanoparticles, magnetic nanoparticles, lipid nanoparticles, and polymer nanoparticles, are utilized in lung cancer treatment [119].

8.1. Hafnium Oxide Nanoparticles (HfO_2 NPs)

Hafnium oxide nanoparticles (HfO_2 NPs) have gained significant attention in cancer treatment as they can be utilized as radiosensitizers in radiotherapy [120]. HfO_2 NPs are used as both radiosensitizers and X-ray contrast agents due to such properties as notable chemical inertness, high dielectric constant, elevated melting point, density, refractive index, transparency to visible light, combined with minimal reactivity in biological systems [121]. HfO_2 NPs are capable of generating high-energy electrons and free radicals upon absorbing high-energy X-ray radiation. Therefore, they are used in the application of X-ray-induced photodynamic therapy (X-PDT). This novel method allows for precise targeting and treatment of deep-seated tumors, thereby improving the overall effectiveness of cancer therapy [122]. NBTXR3 is a type of HfO_2 NP radio-enhancer employed to enhance immune responses in a murine model of metastatic lung cancer resistant to anti-PD1 therapy [123]. NBTXR3 nanoparticles were found to be helpful in treating metastatic lung cancer patients, irrespective of their sensitivity or resistance to immunotherapy [124]. The combination of immune therapy and radiotherapeutic approach using NBTXR3 was shown to elicit noteworthy infiltration and activation of cytotoxic immune cells, leading to robust and enduring immunity in a dual-tumor model of lung cancer in mice [125]. Several clinical trials have been initiated; for example, an ongoing phase I/II clinical trial involves the utilization of HfO_2 NPs in combination with SABR and PD-1 inhibitors to treat metastatic NSCLC patients. Initial results indicate enhanced efficacy, but the trial is currently in the expansion phase [126].

8.2. Magnetic Nanoparticles (MNPs)

Magnetic nanoparticles (MNPs) are made from materials possessing intrinsic magnetic properties, such as iron oxides, cobalt, and nickel. Moreover, MNPs are amenable to functionalization and exhibit significant potential for interventions in targeted drug-delivery platforms for lung cancer by providing substantial drug-loading capacity and efficient penetration into tumors [127]. The main

 doi:10.20944/preprints202401.1751.v1

applications of MNPs are cancer diagnosis, monitoring, and therapy [128]. For instance, loading MNPs with cisplatin was utilized for the treatment of a cisplatin-resistant A549 cancer cell xenograft model, resulting in a notable decrease in the concentration of lung resistance-related proteins, thereby enhancing cisplatin cytotoxicity [129]. Due to their properties, MNPs can be functionalized for highly specific diagnostics applications. For example, superparamagnetic iron oxide nanoparticles (SPIONs) were tested as a T2 contrast agent that enhances the detection of lung cancer metastasis by MRI. SPIONs were functionalized by coating with oleic acid and carboxymethyl dextran and conjugated with an anti-CD44v6 monoclonal antibody that specifically detects metastatic cells [130]. Another example of a T2 MRI contrast agent is nanostructures composed of Fe_3O_4 MNPs with polyelectrolyte layers loaded with doxorubicin hydrochloride chemotherapeutic drug. This nanostructure demonstrated increased cytotoxicity against A549 human lung cancer cells, making it a promising agent for theranostic application [131].

A new approach in lung cancer treatment involves the utilization of MNPs for magnetic hyperthermia through exposure to an external magnetic field that generates thermal effects to eliminate cancer cells [132] [133]. For instance, magnetic iron oxide MNPs were employed to induce localized hyperthermia in lung cancer cells through the application of a pulsed electromagnetic field. The outcomes revealed enhanced cellular uptake by lung cancer cells without causing cytotoxic effects [134]. In conclusion, MNPs, particularly iron oxide nanoparticles like magnetite (Fe_3O_4) or hematite (Fe_2O_3), are considered crucial nanomaterials. They are applied in MRI contrasting, drug delivery, controlled and sustained release, as well as hyperthermia therapy [116].

8.3. Lipid Nanoparticles (LNPs)

Lipid nanoparticles (LNPs) are composed of lipids, which are biocompatible and can encapsulate therapeutic compounds. They can stabilize drugs, enhance their absorption into cells and tissues, and optimize drug delivery to specific target areas. This renders them highly suitable for lung cancer treatment, as they can overcome barriers to drug delivery and improve the overall effectiveness of the treatment [135]. Liposomes, LNPs with an aqueous core surrounded by a lipid bilayer, can be used to encapsulate hydrophilic drugs, such as cisplatin [136]. Liposomal cisplatin has shown promising results in preclinical studies, demonstrating improved drug delivery and enhanced anticancer efficacy compared to free cisplatin [137]. Extensive research has been conducted on LNPs as a promising high specificity targeted delivery tool. A strategy involves employing LNPs to selectively release drugs at designated sites, mimicking the behavior of high-density lipoprotein (HDL). These nanocarriers can be tailored to target specific tumor cells in the lungs, elevating the drug concentration within the tumor while minimizing exposure to healthy tissues. This targeted delivery approach has the potential to enhance treatment efficacy while mitigating potential side effects [135]. Furthermore, LNPs can capitalize on tumors' enhanced permeability and retention (EPR) effect, allowing them to accumulate in tumor tissues preferentially. This passive targeting mechanism can improve drug delivery to the tumor site and increase drug concentration within the tumor. Leveraging the EPR effect, LNPs can potentially improve lung cancer treatment efficiency [138].

Additionally, LNPs offer the advantage of encapsulating drugs with diverse physicochemical properties, including multiple drugs and targeting agents. This facilitates the development of combination therapies addressing various aspects of lung cancer, such as tumor growth, angiogenesis, and metastasis. By integrating multiple drugs into LNPs, there is a potential to amplify the therapeutic impact and overcome drug resistance. For instance, the use of transferrin-functionalized protein-lipid hybrid nanoparticles (PLHNs) containing both cisplatin and docetaxel effectively suppressed the growth of lung tumors in BALB/C mice with lung cancer [139]. Another promising platform strategy involves delivering hydrophilic doxorubicin and hydrophobic paclitaxel to human lung cancer A549 cells through lipid-coated hollow calcium phosphate (LCP) nanoparticles, resulting in heightened antitumor efficacy [140]. A prospective delivery approach for addressing EGFR resistance involved the utilization of a pulmonary microsphere system. This system was applied to simultaneously deliver afatinib and paclitaxel to NSCLC cells resistant to EGFR TKIs

 doi:10.20944/preprints202401.1751.v1

and demonstrated notable effectiveness in the treatment of drug-resistant lung cancer [141]. LNP-mediated targeted delivery can be utilized as a tool for immunotherapy. For instance, the combination of anti-PD-1 antibody with STING agonist-loaded LNPs proved to be more effective than anti-PD-1 monotherapy. This combination led to an augmentation of NK cells in lung metastatic tumors [142].

8.4. Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) are composed of synthetic and natural polymers and have great potential in targeted drug delivery for lung cancer [143]. The unique physiochemical and biological properties of PNPs enhance specific targeting in the body [144]. PNPs composed of polylactic acid (PLA), polyethylene glycol (PEG), poly (lactic-co-glycolic acid) (PLGA), chitosan-loaded lomustine, and biotinylated EGF-conjugated gelatin demonstrated improved drug release, biocompatibility, and increased anticancer effects [145]. In recent research, PNPs have been widely investigated as a potential lung cancer treatment. For instance, nitroimidazole- and hyaluronic acid-based PNPs or PNP-LNP hybrids could efficiently deliver cisplatin to lung cancer cells and xenografts, eliciting a strong antitumor effect with minimal toxicity [146]. Additionally, PEG-PLGA hybrid PNPs were utilized for delivering puerarin and 5-fluorouracil to lung cancer cells, leading to enhanced anticancer effects [147]. Another study also demonstrated that sorafenib-loaded cationically-modified PNPs improved the therapeutic efficacy of sorafenib in NSCLC as compared to the drug alone [148]. In combination treatment, PNPs were employed with a radiosensitizing strategy by combining doxorubicin-loaded polyaspartamide PNPs with 5-aminolevulinic acid to target lung cancer cells. The approach demonstrated selective radiosensitization, resulting in increased efficacy [149]. To enhance the efficacy of localized chemo-radiotherapy for lung cancer, another promising strategy involved the use of folate receptor-targeting multifunctional dual drug-loaded nanoparticles (MDNPs). These nanoparticles featured a poly(N-isopropylacrylamide)-carboxymethyl chitosan shell and a PLGA core, allowing for controlled release of NU7441 radiosensitizer and gemcitabine chemotherapeutic drug. The resulting formulation demonstrated commendable stability, minimal toxicity, and increased efficacy in lung cancer cells [150]. Thus, PNPs represent a promising strategy for lung cancer treatment characterized by increased efficacy with minimal toxicity.

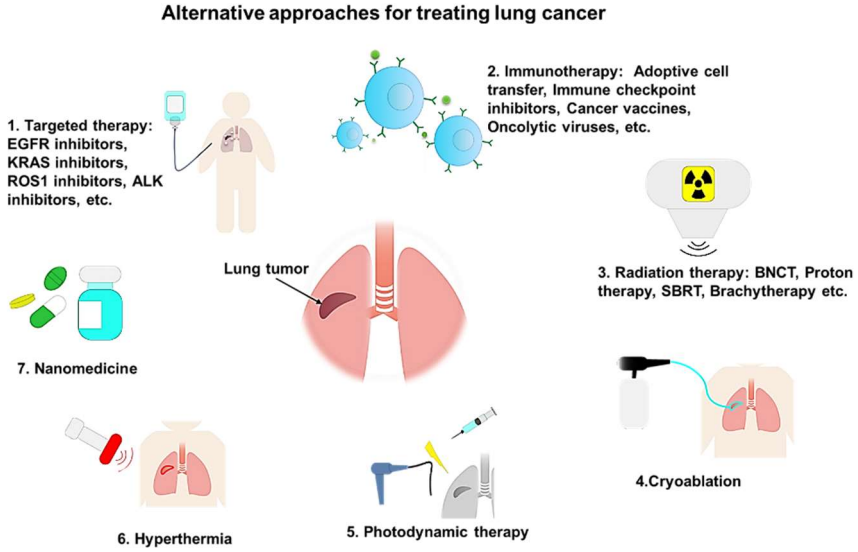

Figure 4. Lung cancer emerging treatments are Targeted therapy, Immunotherapy, Radiation therapy, Cryoablation, Photodynamic therapy, Hyperthermia, and Nanomedicine.

9. Conclusion

In summary, the field of lung cancer treatment is experiencing a profound transformation marked by the introduction of groundbreaking therapies. Advancements in personalized medicine, targeted therapies, and immunotherapy provide new hope for patients with this challenging disease.

These cutting-edge treatments have allowed for tailored therapy that improves patient outcomes and diminishes the adverse effects of traditional interventions. As scientific research delves deeper into the intricacies of the disease, the ongoing advancements in emerging lung cancer treatments hold the potential to reshape the standard of care.

Author Contributions: writing—original draft preparation, A.S.L.; writing—review and editing, A. S.L. and S.-H.C.; supervision, S.-H.C.; funding acquisition, S.-H.C. All authors have read and agreed to the published version of the manuscript."

Funding: Funding: This study was funded by the Ministry of Science and Technology, Taiwan (NSTC111-2320-B-A49-028-MY3), Taipei Veterans General Hospital (113VACS-007 and V113E-005-1), the IBMS CRC Research Program of the Institute of Biomedical Sciences, Academia Sinica, Taiwan (IBMS-CRC112-P03), " Center for Intelligent Drug Systems and Smart Bio-devices (IDS2B) " from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan, Higher Education SPROUT project for Cancer Progression Research Center (111W31101) and Cancer and Immunology Research Center, Taiwan (112W31101).

Acknowledgments: We would like to express our thanks to Ph.D I-Chieh Wang for assisting us in completing the administrative procedures.

Conflicts of Interest:. The authors declare that they have no potential conflicts of interest in the present study.

References

1. Fu F, Chen Z, Chen H. Treating lung cancer: defining surgical curative time window. Cell Res. 2023;33(9):649-50. doi: 10.1038/s41422-023-00852-w. PubMed PMID: 37479857; PubMed Central PMCID: PMCPMC10474008.
2. Li C, Wang H, Jiang Y, Fu W, Liu X, Zhong R, et al. Advances in lung cancer screening and early detection. Cancer Biol Med. 2022;19(5):591-608. Epub 20220511. doi: 10.20892/j.issn.2095-3941.2021.0690. PubMed PMID: 35535966; PubMed Central PMCID: PMCPMC9196057.
3. Nam MW, Kim CW, Choi KC. Epithelial-Mesenchymal Transition-Inducing Factors Involved in the Progression of Lung Cancers. Biomol Ther (Seoul). 2022;30(3):213-20. doi: 10.4062/biomolther.2021.178. PubMed PMID: 35039464; PubMed Central PMCID: PMCPMC9047489.
4. Tang S, Qin C, Hu H, Liu T, He Y, Guo H, et al. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. Cells. 2022;11(3). Epub 20220119. doi: 10.3390/cells11030320. PubMed PMID: 35159131; PubMed Central PMCID: PMCPMC8834198.
5. Lahiri A, Maji A, Potdar PD, Singh N, Parikh P, Bisht B, et al. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer. 2023;22(1):40. Epub 20230221. doi: 10.1186/s12943-023-01740-y. PubMed PMID: 36810079; PubMed Central PMCID: PMCPMC9942077.
6. Koinis F, Kotsakis A, Georgoulias V. Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res. 2016;5(1):39-50. doi: 10.3978/j.issn.2218-6751.2016.01.03. PubMed PMID: 26958492; PubMed Central PMCID: PMCPMC4758968.
7. Li S, de Camargo Correia GS, Wang J, Manochakian R, Zhao Y, Lou Y. Emerging Targeted Therapies in Advanced Non-Small-Cell Lung Cancer. Cancers (Basel). 2023;15(11). Epub 20230524. doi: 10.3390/cancers15112899. PubMed PMID: 37296863; PubMed Central PMCID: PMCPMC10251928.
8. Wang Z, Xing Y, Li B, Li X, Liu B, Wang Y. Molecular pathways, resistance mechanisms and targeted interventions in non-small-cell lung cancer. Mol Biomed. 2022;3(1):42. Epub 20221212. doi: 10.1186/s43556-022-00107-x. PubMed PMID: 36508072; PubMed Central PMCID: PMCPMC9743956.
9. Shi K, Wang G, Pei J, Zhang J, Wang J, Ouyang L, et al. Emerging strategies to overcome resistance to third-generation EGFR inhibitors. J Hematol Oncol. 2022;15(1):94. Epub 20220715. doi: 10.1186/s13045-022-01311-6. PubMed PMID: 35840984; PubMed Central PMCID: PMCPMC9287895.
10. Ricordel C, Friboulet L, Facchinetti F, Soria JC. Molecular mechanisms of acquired resistance to third-generation EGFR-TKIs in EGFR T790M-mutant lung cancer. Ann Oncol. 2018;29(suppl_1):i28-i37. doi: 10.1093/annonc/mdx705. PubMed PMID: 29462256.
11. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-25. Epub 20171118. doi: 10.1056/NEJMoa1713137. PubMed PMID: 29151359.
12. Lim S, Ahn J, Hong M-H, Kim T, Jung H-A, Ou S-H, et al. MA07. 09 BBT-176, a 4th generation EGFR TKI, for Progressed NSCLC after EGFR TKI Therapy: PK, Safety and Efficacy from Phase 1 Study. Journal of Thoracic Oncology. 2022;17(9):S70-S1.
13. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised

phase III trial. Lancet. 2009;373(9674):1525-31. doi: 10.1016/s0140-6736(09)60569-9. PubMed PMID: 19410716.
14. Khambata-Ford S, Harbison CT, Hart LL, Awad M, Xu LA, Horak CE, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(6):918-27. Epub 20100125. doi: 10.1200/jco.2009.25.2890. PubMed PMID: 20100958.
15. Cho BC, Simi A, Sabari J, Vijayaraghavan S, Moores S, Spira A. Amivantamab, an Epidermal Growth Factor Receptor (EGFR) and Mesenchymal-epithelial Transition Factor (MET) Bispecific Antibody, Designed to Enable Multiple Mechanisms of Action and Broad Clinical Applications. Clinical Lung Cancer. 2023;24(2):89-97. doi: https://doi.org/10.1016/j.cllc.2022.11.004.
16. Cho B, Lee K, Cho E, Kim D, Lee J, Han J, et al. 1258O Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC. Annals of Oncology. 2020;31:S813.
17. Zhou F, Zhou CC. Targeted therapies for patients with advanced NSCLC harboring wild-type EGFR: what's new and what's enough. Chin J Cancer. 2015;34(7):310-9. Epub 20150718. doi: 10.1186/s40880-015-0036-4. PubMed PMID: 26187152; PubMed Central PMCID: PMCPMC4593374.
18. Araghi M, Mannani R, Heidarnejad Maleki A, Hamidi A, Rostami S, Safa SH, et al. Recent advances in non-small cell lung cancer targeted therapy; an update review. Cancer Cell Int. 2023;23(1):162. Epub 20230811. doi: 10.1186/s12935-023-02990-y. PubMed PMID: 37568193; PubMed Central PMCID: PMCPMC10416536.
19. Goebel L, Müller MP, Goody RS, Rauh D. KRasG12C inhibitors in clinical trials: a short historical perspective. RSC Med Chem. 2020;11(7):760-70. Epub 20200601. doi: 10.1039/d0md00096e. PubMed PMID: 33479673; PubMed Central PMCID: PMCPMC7549139.
20. O'Sullivan É, Keogh A, Henderson B, Finn SP, Gray SG, Gately K. Treatment Strategies for KRAS-Mutated Non-Small-Cell Lung Cancer. Cancers (Basel). 2023;15(6). Epub 20230307. doi: 10.3390/cancers15061635. PubMed PMID: 36980522; PubMed Central PMCID: PMCPMC10046549.
21. McCormick F. KRAS as a Therapeutic Target. Clin Cancer Res. 2015;21(8):1797-801. doi: 10.1158/1078-0432.Ccr-14-2662. PubMed PMID: 25878360; PubMed Central PMCID: PMCPMC4407814.
22. FDA Approves First KRAS Inhibitor: Sotorasib. Cancer Discov. 2021;11(8):Of4. Epub 20210622. doi: 10.1158/2159-8290.Cd-nb2021-0362. PubMed PMID: 34158284.
23. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. N Engl J Med. 2021;384(25):2371-81. Epub 20210604. doi: 10.1056/NEJMoa2103695. PubMed PMID: 34096690; PubMed Central PMCID: PMCPMC9116274.
24. Gort E, Johnson ML, Hwang JJ, Pant S, Dünzinger U, Riemann K, et al. A phase I, open-label, dose-escalation trial of BI 1701963 as monotherapy and in combination with trametinib in patients with KRAS mutated advanced or metastatic solid tumors. J Clin Oncol. 2020;38(15 Suppl).
25. Palma G, Khurshid F, Lu K, Woodward B, Husain H. Selective KRAS G12C inhibitors in non-small cell lung cancer: chemistry, concurrent pathway alterations, and clinical outcomes. NPJ Precis Oncol. 2021;5(1):98. Epub 20211129. doi: 10.1038/s41698-021-00237-5. PubMed PMID: 34845311; PubMed Central PMCID: PMCPMC8630042.
26. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141(7):1117-34. doi: 10.1016/j.cell.2010.06.011. PubMed PMID: 20602996; PubMed Central PMCID: PMCPMC2914105.
27. Tan DS, Araújo A, Zhang J, Signorovitch J, Zhou ZY, Cai X, et al. Comparative Efficacy of Ceritinib and Crizotinib as Initial ALK-Targeted Therapies in Previously Treated Advanced NSCLC: An Adjusted Comparison with External Controls. J Thorac Oncol. 2016;11(9):1550-7. Epub 20160608. doi: 10.1016/j.jtho.2016.05.029. PubMed PMID: 27288979.
28. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol. 2017;18(12):1590-9. Epub 20171023. doi: 10.1016/s1470-2045(17)30680-0. PubMed PMID: 29074098; PubMed Central PMCID: PMCPMC5777233.
29. Cui JJ, Tran-Dubé M, Shen H, Nambu M, Kung PP, Pairish M, et al. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem. 2011;54(18):6342-63. Epub 20110818. doi: 10.1021/jm2007613. PubMed PMID: 21812414.
30. Huang Z, Xiong Q, Cui Z, Tao H, Zhang S, Wang L, et al. Efficacy and safety of crizotinib plus bevacizumab in ALK/ROS-1/c-MET positive non-small cell lung cancer: an open-label, single-arm, prospective observational study. Am J Transl Res. 2021;13(3):1526-34. Epub 20210315. PubMed PMID: 33841676; PubMed Central PMCID: PMCPMC8014364.
31. Felip E, Kim D, Mehra R, Tan DS, Chow L, Camidge DR, et al. Efficacy and safety of ceritinib in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): an update of ASCEND-1. Annals of Oncology. 2014;25:iv456.

32. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167-77. doi: 10.1056/NEJMoa1408440. PubMed PMID: 25470694.
33. Yang J-J, Zhou J, Cheng Y, Li M, Zhao Q, Zhang Z, et al. SAF-189s in advanced, ALK-positive, non–small cell lung cancer: Results from a first-in-human phase 1/2, multicenter study. American Society of Clinical Oncology; 2022.
34. Zhao H, Chen J, Song Z, Zhao Y, Guo Y, Wu G, et al. First-in-human phase I results of APG-2449, a novel FAK and third-generation ALK/ROS1 tyrosine kinase inhibitor (TKI), in patients (pts) with second-generation TKI-resistant ALK/ROS1+ non–small cell lung cancer (NSCLC) or mesothelioma. American Society of Clinical Oncology; 2022.
35. Davies KD, Doebele RC. Molecular pathways: ROS1 fusion proteins in cancer. Clin Cancer Res. 2013;19(15):4040-5. Epub 20130529. doi: 10.1158/1078-0432.Ccr-12-2851. PubMed PMID: 23719267; PubMed Central PMCID: PMCPMC3732549.
36. Lin JJ, Cho BC, Springfeld C, Camidge DR, Solomon B, Baik C, et al. Abstract P224: Update from the Phase 2 registrational trial of repotrectinib in TKI-pretreated patients with ROS1+ advanced non-small cell lung cancer and with NTRK+ advanced solid tumors (TRIDENT-1). Molecular Cancer Therapeutics. 2021;20(12_Supplement):P224-P.
37. Li W, Yang N, Ma H, Fan H, Li K, Wu H, et al. The efficacy and safety of taletrectinib in patients with TKI-naïve or crizotinib-pretreated ROS1-positive non–small cell lung cancer (NSCLC). American Society of Clinical Oncology; 2022.
38. Liu D, Che X, Wang X, Ma C, Wu G. Tumor Vaccines: Unleashing the Power of the Immune System to Fight Cancer. Pharmaceuticals (Basel). 2023;16(10). Epub 20230929. doi: 10.3390/ph16101384. PubMed PMID: 37895855; PubMed Central PMCID: PMCPMC10610367.
39. Gupta SL, Basu S, Soni V, Jaiswal RK. Immunotherapy: an alternative promising therapeutic approach against cancers. Mol Biol Rep. 2022;49(10):9903-13. Epub 20220627. doi: 10.1007/s11033-022-07525-8. PubMed PMID: 35759082; PubMed Central PMCID: PMCPMC9244230.
40. Miao L, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. Mol Cancer. 2021;20(1):41. Epub 20210225. doi: 10.1186/s12943-021-01335-5. PubMed PMID: 33632261; PubMed Central PMCID: PMCPMC7905014.
41. Rosenberg SA, Parkhurst MR, Robbins PF. Adoptive cell transfer immunotherapy for patients with solid epithelial cancers. Cancer Cell. 2023;41(4):646-8. doi: 10.1016/j.ccell.2023.03.003. PubMed PMID: 37037613; PubMed Central PMCID: PMCPMC10184665.
42. Chocarro L, Arasanz H, Fernández-Rubio L, Blanco E, Echaide M, Bocanegra A, et al. CAR-T Cells for the Treatment of Lung Cancer. Life (Basel). 2022;12(4). Epub 20220408. doi: 10.3390/life12040561. PubMed PMID: 35455052; PubMed Central PMCID: PMCPMC9028981.
43. Zhong S, Cui Y, Liu Q, Chen S. CAR-T cell therapy for lung cancer: a promising but challenging future. J Thorac Dis. 2020;12(8):4516-21. doi: 10.21037/jtd.2020.03.118. PubMed PMID: 32944366; PubMed Central PMCID: PMCPMC7475572.
44. Wang S, Sun J, Chen K, Ma P, Lei Q, Xing S, et al. Perspectives of tumor-infiltrating lymphocyte treatment in solid tumors. BMC Med. 2021;19(1):140. Epub 20210611. doi: 10.1186/s12916-021-02006-4. PubMed PMID: 34112147; PubMed Central PMCID: PMCPMC8194199.
45. Paluch C, Santos AM, Anzilotti C, Cornall RJ, Davis SJ. Immune Checkpoints as Therapeutic Targets in Autoimmunity. Front Immunol. 2018;9:2306. Epub 20181008. doi: 10.3389/fimmu.2018.02306. PubMed PMID: 30349540; PubMed Central PMCID: PMCPMC6186808.
46. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune Checkpoint Inhibitors in Cancer Therapy. Curr Oncol. 2022;29(5):3044-60. Epub 20220424. doi: 10.3390/curroncol29050247. PubMed PMID: 35621637; PubMed Central PMCID: PMCPMC9139602.
47. Huang T, Liu L, Lv Z, Zhao K, Yi Q, Zhang J. Recent Advances in DNA Vaccines against Lung Cancer: A Mini Review. Vaccines (Basel). 2022;10(10). Epub 20220921. doi: 10.3390/vaccines10101586. PubMed PMID: 36298450; PubMed Central PMCID: PMCPMC9612219.
48. Lin MJ, Svensson-Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD, et al. Cancer vaccines: the next immunotherapy frontier. Nat Cancer. 2022;3(8):911-26. Epub 20220823. doi: 10.1038/s43018-022-00418-6. PubMed PMID: 35999309.
49. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Silva Souza JV, Rocha Pinheiro SL, et al. Oncolytic virus therapy in cancer: A current review. World J Virol. 2021;10(5):229-55. doi: 10.5501/wjv.v10.i5.229. PubMed PMID: 34631474; PubMed Central PMCID: PMCPMC8474975.
50. Sakhi H, Arabi M, Ghaemi A, Movafagh A, Sheikhpour M. Oncolytic viruses in lung cancer treatment: a review article. Immunotherapy. 2024;16(2):75-97. Epub 20231219. doi: 10.2217/imt-2023-0124. PubMed PMID: 38112057.

51. Lin D, Shen Y, Liang T. Oncolytic virotherapy: basic principles, recent advances and future directions. Signal Transduct Target Ther. 2023;8(1):156. Epub 20230411. doi: 10.1038/s41392-023-01407-6. PubMed PMID: 37041165; PubMed Central PMCID: PMCPMC10090134.
52. Malhotra J, Kim ES. Oncolytic Viruses and Cancer Immunotherapy. Curr Oncol Rep. 2023;25(1):19-28. Epub 20221128. doi: 10.1007/s11912-022-01341-w. PubMed PMID: 36441447.
53. Wang S, Zhang Z, Miao L, Li Y. Boron Neutron Capture Therapy: Current Status and Challenges. Front Oncol. 2022;12:788770. Epub 20220331. doi: 10.3389/fonc.2022.788770. PubMed PMID: 35433432; PubMed Central PMCID: PMCPMC9009440.
54. Trivillin VA, Garabalino MA, Colombo LL, González SJ, Farías RO, Monti Hughes A, et al. Biodistribution of the boron carriers boronophenylalanine (BPA) and/or decahydrodecaborate (GB-10) for Boron Neutron Capture Therapy (BNCT) in an experimental model of lung metastases. Appl Radiat Isot. 2014;88:94-8. Epub 20131205. doi: 10.1016/j.apradiso.2013.11.115. PubMed PMID: 24360862.
55. Trivillin VA, Serrano A, Garabalino MA, Colombo LL, Pozzi EC, Hughes AM, et al. Translational boron neutron capture therapy (BNCT) studies for the treatment of tumors in lung. Int J Radiat Biol. 2019;95(5):646-54. Epub 20190222. doi: 10.1080/09553002.2019.1564080. PubMed PMID: 30601686.
56. Andoh T, Fujimoto T, Suzuki M, Sudo T, Sakurai Y, Tanaka H, et al. Boron neutron capture therapy (BNCT) as a new approach for clear cell sarcoma (CCS) treatment: Trial using a lung metastasis model of CCS. Appl Radiat Isot. 2015;106:195-201. Epub 20150821. doi: 10.1016/j.apradiso.2015.07.060. PubMed PMID: 26337135.
57. Alberti D, Protti N, Toppino A, Deagostino A, Lanzardo S, Bortolussi S, et al. A theranostic approach based on the use of a dual boron/Gd agent to improve the efficacy of Boron Neutron Capture Therapy in the lung cancer treatment. Nanomedicine. 2015;11(3):741-50. Epub 20150114. doi: 10.1016/j.nano.2014.12.004. PubMed PMID: 25596074.
58. Kiger JL, Kiger WS, Patel H, Binns PJ, Riley KJ, Hopewell JW, et al. Effects of boron neutron capture irradiation on the normal lung of rats. Appl Radiat Isot. 2004;61(5):969-73. doi: 10.1016/j.apradiso.2004.05.021. PubMed PMID: 15308177.
59. Suzuki M, Suzuki O, Sakurai Y, Tanaka H, Kondo N, Kinashi Y, et al. Reirradiation for locally recurrent lung cancer in the chest wall with boron neutron capture therapy (BNCT). International Cancer Conference Journal. 2012;1(4):235-8. doi: 10.1007/s13691-012-0048-8.
60. Masunaga SI, Sakurai Y, Tanaka H, Takata T, Suzuki M, Sanada Y, et al. Usefulness of combination with both continuous administration of hypoxic cytotoxin and mild temperature hyperthermia in boron neutron capture therapy in terms of local tumor response and lung metastatic potential. Int J Radiat Biol. 2019;95(12):1708-17. Epub 20190923. doi: 10.1080/09553002.2019.1666214. PubMed PMID: 31545117.
61. Yu H, Tang X, Shu D, Liu Y, Geng C, Gong C, et al. Influence of Neutron Sources and 10B Concentration on Boron Neutron Capture Therapy for Shallow and Deeper Non-small Cell Lung Cancer. Health Phys. 2017;112(3):258-65. doi: 10.1097/hp.0000000000000601. PubMed PMID: 28121726.
62. Suzuki M, Sakurai Y, Masunaga S, Kinashi Y, Nagata K, Maruhashi A, et al. Feasibility of boron neutron capture therapy (BNCT) for malignant pleural mesothelioma from a viewpoint of dose distribution analysis. Int J Radiat Oncol Biol Phys. 2006;66(5):1584-9. Epub 20061023. doi: 10.1016/j.ijrobp.2006.08.026. PubMed PMID: 17056195.
63. Han Y. Current status of proton therapy techniques for lung cancer. Radiat Oncol J. 2019;37(4):232-48. Epub 20191231. doi: 10.3857/roj.2019.00633. PubMed PMID: 31918460; PubMed Central PMCID: PMCPMC6952710.
64. Vyfhuis MAL, Onyeuku N, Diwanji T, Mossahebi S, Amin NP, Badiyan SN, et al. Advances in proton therapy in lung cancer. Ther Adv Respir Dis. 2018;12:1753466618783878. doi: 10.1177/1753466618783878. PubMed PMID: 30014783; PubMed Central PMCID: PMCPMC6050808.
65. Register SP, Zhang X, Mohan R, Chang JY. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;80(4):1015-22. Epub 20100707. doi: 10.1016/j.ijrobp.2010.03.012. PubMed PMID: 20615629; PubMed Central PMCID: PMCPMC2952351.
66. Giaddui T, Chen W, Yu J, Lin L, Simone CB, 2nd, Yuan L, et al. Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: phase III randomized trial comparing overall survival after photon versus proton radiochemotherapy for inoperable stage II-IIIB NSCLC. Radiat Oncol. 2016;11:66. Epub 20160504. doi: 10.1186/s13014-016-0640-8. PubMed PMID: 27142674; PubMed Central PMCID: PMCPMC4855766.
67. Zschaeck S, Simon M, Löck S, Troost EG, Stützer K, Wohlfahrt P, et al. PRONTOX - proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung carcinomas (NSCLC): study protocol for a randomised controlled trial. Trials. 2016;17(1):543. Epub 20161115. doi: 10.1186/s13063-016-1679-4. PubMed PMID: 27846903; PubMed Central PMCID: PMCPMC5111266.
68. Andruska N, Stowe HB, Crockett C, Liu W, Palma D, Faivre-Finn C, et al. Stereotactic Radiation for Lung Cancer: A Practical Approach to Challenging Scenarios. J Thorac Oncol. 2021;16(7):1075-85. Epub 20210424. doi: 10.1016/j.jtho.2021.04.002. PubMed PMID: 33901637.

69. Lo SS, Loblaw A, Chang EL, Mayr NA, Teh BS, Huang Z, et al. Emerging applications of stereotactic body radiotherapy. Future Oncol. 2014;10(7):1299-310. doi: 10.2217/fon.14.13. PubMed PMID: 24947266.
70. Milano MT, Kong FS, Movsas B. Stereotactic body radiotherapy as salvage treatment for recurrence of non-small cell lung cancer after prior surgery or radiotherapy. Transl Lung Cancer Res. 2019;8(1):78-87. doi: 10.21037/tlcr.2018.08.15. PubMed PMID: 30788237; PubMed Central PMCID: PMCPMC6351395.
71. Hou Y, Hermann G, Lewis JH, Aerts HJ, Baldini EH, Chen AB, et al. Clinical Outcomes After Lung Stereotactic Body Radiation Therapy in Patients With or Without a Prior Lung Resection. Am J Clin Oncol. 2018;41(7):695-701. doi: 10.1097/coc.0000000000000344. PubMed PMID: 27819875.
72. Prezzano KM, Ma SJ, Hermann GM, Rivers CI, Gomez-Suescun JA, Singh AK. Stereotactic body radiation therapy for non-small cell lung cancer: A review. World J Clin Oncol. 2019;10(1):14-27. doi: 10.5306/wjco.v10.i1.14. PubMed PMID: 30627522; PubMed Central PMCID: PMCPMC6318482.
73. Vlaskou Badra E, Baumgartl M, Fabiano S, Jongen A, Guckenberger M. Stereotactic radiotherapy for early stage non-small cell lung cancer: current standards and ongoing research. Transl Lung Cancer Res. 2021;10(4):1930-49. doi: 10.21037/tlcr-20-860. PubMed PMID: 34012804; PubMed Central PMCID: PMCPMC8107760.
74. Mayer C, Gasalberti DP, Kumar A. Brachytherapy. StatPearls. Treasure Island (FL): StatPearls Publishing
75. Copyright © 2023, StatPearls Publishing LLC.; 2023.
76. Qiu B, Jiang P, Ji Z, Huo X, Sun H, Wang J. Brachytherapy for lung cancer. Brachytherapy. 2021;20(2):454-66. doi: https://doi.org/10.1016/j.brachy.2020.11.009.
77. Skowronek J. Brachytherapy in the treatment of lung cancer - a valuable solution. J Contemp Brachytherapy. 2015;7(4):297-311. Epub 20150914. doi: 10.5114/jcb.2015.54038. PubMed PMID: 26622233; PubMed Central PMCID: PMCPMC4643732.
78. Singh DP, Aujla K, Nead M, Bylund K. Radiologically Occult Lung Cancer Curatively Treated with High-Dose Rate Endobronchial Brachytherapy. J Clin Imaging Sci. 2021;11:45. Epub 20210823. doi: 10.25259/jcis_134_2021. PubMed PMID: 34513209; PubMed Central PMCID: PMCPMC8422503.
79. Hosni A, Bezjak A, Rink A, Czarnecka K, McPartlin A, Patterson S, et al. High Dose Rate Brachytherapy as a Treatment Option in Endobronchial Tumors. Lung Cancer Int. 2016;2016:3086148. Epub 20160714. doi: 10.1155/2016/3086148. PubMed PMID: 27493804; PubMed Central PMCID: PMCPMC4963588.
80. Sabrià PT, Rosinés JM, López-Lisbona M, De Frutos NC, Díez-Ferrer M, Sanchez SP, et al. P2. 18-13 Endobronchial Brachytherapy: A Single Institutional Experience. Journal of Thoracic Oncology. 2019;14(10):S907-S8.
81. Sur R, Pond G, Falkson C, Pan M, Wright J, Bezjak A, et al. BRACHY: A Randomized Trial to Evaluate Symptom Improvement in Advanced Non-Small Cell Lung Cancer Treated With External Beam Radiation With or Without High-Dose-Rate Intraluminal Brachytherapy. Int J Radiat Oncol Biol Phys. 2023;116(3):601-10. Epub 20230105. doi: 10.1016/j.ijrobp.2022.12.049. PubMed PMID: 36610615.
82. Niu L, Xu K, Mu F. Cryosurgery for lung cancer. J Thorac Dis. 2012;4(4):408-19. doi: 10.3978/j.issn.2072-1439.2012.07.13. PubMed PMID: 22934144; PubMed Central PMCID: PMCPMC3426750.
83. Medlej ZAA, Medlej W, Slaba S, Torrecillas P, Cueto A, Urbaneja A, et al. Cryoablation and Immunotherapy: An Enthralling Synergy for Cancer Treatment. Curr Oncol. 2023;30(5):4844-60. Epub 20230508. doi: 10.3390/curroncol30050365. PubMed PMID: 37232823; PubMed Central PMCID: PMCPMC10217386.
84. Velez A, DeMaio A, Sterman D. Cryoablation and immunity in non-small cell lung cancer: a new era of cryo-immunotherapy. Front Immunol. 2023;14:1203539. Epub 20230821. doi: 10.3389/fimmu.2023.1203539. PubMed PMID: 37671163; PubMed Central PMCID: PMCPMC10475831.
85. Uhlschmid G, Kolb E, Largiadèr F. Cryosurgery of pulmonary metastases. Cryobiology. 1979;16(2):171-8. doi: 10.1016/0011-2240(79)90028-2. PubMed PMID: 477364.
86. Lin M, Liang SZ, Wang XH, Liang YQ, Zhang MJ, Niu LZ, et al. Clinical efficacy of percutaneous cryoablation combined with allogenic NK cell immunotherapy for advanced non-small cell lung cancer. Immunol Res. 2017;65(4):880-7. doi: 10.1007/s12026-017-8927-x. PubMed PMID: 28508945.
87. Gu XY, Jiang Z, Fang W. Cryoablation combined with molecular target therapy improves the curative effect in patients with advanced non-small cell lung cancer. J Int Med Res. 2011;39(5):1736-43. doi: 10.1177/147323001103900516. PubMed PMID: 22117974.
88. Das SK, Huang YY, Li B, Yu XX, Xiao RH, Yang HF. Comparing cryoablation and microwave ablation for the treatment of patients with stage IIIB/IV non-small cell lung cancer. Oncol Lett. 2020;19(1):1031-41. Epub 20191125. doi: 10.3892/ol.2019.11149. PubMed PMID: 31885721; PubMed Central PMCID: PMCPMC6924207.
89. Mokwena MG, Kruger CA, Ivan MT, Heidi A. A review of nanoparticle photosensitizer drug delivery uptake systems for photodynamic treatment of lung cancer. Photodiagnosis Photodyn Ther. 2018;22:147-54. Epub 20180326. doi: 10.1016/j.pdpdt.2018.03.006. PubMed PMID: 29588217.
90. Baptista MS, Cadet J, Di Mascio P, Ghogare AA, Greer A, Hamblin MR, et al. Type I and Type II Photosensitized Oxidation Reactions: Guidelines and Mechanistic Pathways. Photochem Photobiol.

2017;93(4):912-9. Epub 20170327. doi: 10.1111/php.12716. PubMed PMID: 28084040; PubMed Central PMCID: PMCPMC5500392.

91. Ma QL, Shen MO, Han N, Xu HZ, Peng XC, Li QR, et al. Chlorin e6 mediated photodynamic therapy triggers resistance through ATM-related DNA damage response in lung cancer cells. Photodiagnosis Photodyn Ther. 2022;37:102645. Epub 20211123. doi: 10.1016/j.pdpdt.2021.102645. PubMed PMID: 34823034.
92. Wang K, Yu B, Pathak JL. An update in clinical utilization of photodynamic therapy for lung cancer. J Cancer. 2021;12(4):1154-60. Epub 20210101. doi: 10.7150/jca.51537. PubMed PMID: 33442413; PubMed Central PMCID: PMCPMC7797657.
93. Maziak DE, Markman BR, MacKay JA, Evans WK. Photodynamic therapy in nonsmall cell lung cancer: a systematic review. Ann Thorac Surg. 2004;77(4):1484-91. doi: 10.1016/j.athoracsur.2003.07.017. PubMed PMID: 15063303.
94. Shafirstein G, Battoo A, Harris K, Baumann H, Gollnick SO, Lindenmann J, et al. Photodynamic Therapy of Non-Small Cell Lung Cancer. Narrative Review and Future Directions. Ann Am Thorac Soc. 2016;13(2):265-75. doi: 10.1513/AnnalsATS.201509-650FR. PubMed PMID: 26646726; PubMed Central PMCID: PMCPMC5015713.
95. Crous A, Abrahamse H. Photodynamic therapy of lung cancer, where are we? Front Pharmacol. 2022;13:932098. Epub 20220830. doi: 10.3389/fphar.2022.932098. PubMed PMID: 36110552; PubMed Central PMCID: PMCPMC9468662.
96. Olszowy M, Nowak-Perlak M, Woźniak M. Current Strategies in Photodynamic Therapy (PDT) and Photodynamic Diagnostics (PDD) and the Future Potential of Nanotechnology in Cancer Treatment. Pharmaceutics. 2023;15(6). Epub 20230612. doi: 10.3390/pharmaceutics15061712. PubMed PMID: 37376160; PubMed Central PMCID: PMCPMC10301405.
97. Kumari P, Rompicharla SVK, Bhatt H, Ghosh B, Biswas S. Development of chlorin e6-conjugated poly(ethylene glycol)-poly(d,l-lactide) nanoparticles for photodynamic therapy. Nanomedicine (Lond). 2019;14(7):819-34. Epub 20190315. doi: 10.2217/nnm-2018-0255. PubMed PMID: 30874479.
98. Cao W, Liu B, Xia F, Duan M, Hong Y, Niu J, et al. MnO(2)@Ce6-loaded mesenchymal stem cells as an "oxygen-laden guided-missile" for the enhanced photodynamic therapy on lung cancer. Nanoscale. 2020;12(5):3090-102. doi: 10.1039/c9nr07947e. PubMed PMID: 31965129.
99. Kimura M, Miyajima K, Kojika M, Kono T, Kato H. Photodynamic Therapy (PDT) with Chemotherapy for Advanced Lung Cancer with Airway Stenosis. Int J Mol Sci. 2015;16(10):25466-75. Epub 20151023. doi: 10.3390/ijms161025466. PubMed PMID: 26512656; PubMed Central PMCID: PMCPMC4632810.
100. Ji W, Yoo JW, Bae EK, Lee JH, Choi CM. The effect of Radachlorin® PDT in advanced NSCLC: a pilot study. Photodiagnosis Photodyn Ther. 2013;10(2):120-6. Epub 20130316. doi: 10.1016/j.pdpdt.2013.01.004. PubMed PMID: 23769277.
101. Dhillon SS, Demmy TL, Yendamuri S, Loewen G, Nwogu C, Cooper M, et al. A Phase I Study of Light Dose for Photodynamic Therapy Using 2-[1-Hexyloxyethyl]-2 Devinyl Pyropheophorbide-a for the Treatment of Non-Small Cell Carcinoma In Situ or Non-Small Cell Microinvasive Bronchogenic Carcinoma: A Dose Ranging Study. J Thorac Oncol. 2016;11(2):234-41. Epub 20151222. doi: 10.1016/j.jtho.2015.10.020. PubMed PMID: 26718878; PubMed Central PMCID: PMCPMC4729686.
102. Weinberg BD, Allison RR, Sibata C, Parent T, Downie G. Results of combined photodynamic therapy (PDT) and high dose rate brachytherapy (HDR) in treatment of obstructive endobronchial non-small cell lung cancer (NSCLC). Photodiagnosis Photodyn Ther. 2010;7(1):50-8. Epub 20091229. doi: 10.1016/j.pdpdt.2009.12.002. PubMed PMID: 20230994.
103. Sonokawa T, Obi N, Usuda J, Sudo Y, Hamakubo T. Development of a new minimally invasive phototherapy for lung cancer using antibody-toxin conjugate. Thorac Cancer. 2023;14(7):645-53. Epub 20230119. doi: 10.1111/1759-7714.14776. PubMed PMID: 36655546; PubMed Central PMCID: PMCPMC9981311.
104. Dunne M, Regenold M, Allen C. Hyperthermia can alter tumor physiology and improve chemo- and radiotherapy efficacy. Adv Drug Deliv Rev. 2020;163-164:98-124. Epub 20200715. doi: 10.1016/j.addr.2020.07.007. PubMed PMID: 32681862.
105. Oei AL, Vriend LE, Crezee J, Franken NA, Krawczyk PM. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiat Oncol. 2015;10:165. Epub 20150807. doi: 10.1186/s13014-015-0462-0. PubMed PMID: 26245485; PubMed Central PMCID: PMCPMC4554295.
106. Yang WH, Xie J, Lai ZY, Yang MD, Zhang GH, Li Y, et al. Radiofrequency deep hyperthermia combined with chemotherapy in the treatment of advanced non-small cell lung cancer. Chin Med J (Engl). 2019;132(8):922-7. doi: 10.1097/cm9.0000000000000156. PubMed PMID: 30958433; PubMed Central PMCID: PMCPMC6595762.
107. Cherukuri P, Glazer ES, Curley SA. Targeted hyperthermia using metal nanoparticles. Adv Drug Deliv Rev. 2010;62(3):339-45. Epub 20091110. doi: 10.1016/j.addr.2009.11.006. PubMed PMID: 19909777; PubMed Central PMCID: PMCPMC2827640.

108. Vertrees RA, Das GC, Coscio AM, Xie J, Zwischenberger JB, Boor PJ. A mechanism of hyperthermia-induced apoptosis in ras-transformed lung cells. Mol Carcinog. 2005;44(2):111-21. doi: 10.1002/mc.20124. PubMed PMID: 16114053.
109. Lee H, Kim S, Choi BH, Park MT, Lee J, Jeong SY, et al. Hyperthermia improves therapeutic efficacy of doxorubicin carried by mesoporous silica nanocontainers in human lung cancer cells. Int J Hyperthermia. 2011;27(7):698-707. doi: 10.3109/02656736.2011.608217. PubMed PMID: 21992562.
110. Hazan G, Lurie H, Yerushalmi A. Sensitization of combined cis-platinum and cyclophosphamide by local hyperthermia in mice bearing the Lewis lung carcinoma. Oncology. 1984;41(1):68-9. doi: 10.1159/000225794. PubMed PMID: 6538329.
111. Spirou SV, Basini M, Lascialfari A, Sangregorio C, Innocenti C. Magnetic Hyperthermia and Radiation Therapy: Radiobiological Principles and Current Practice (†). Nanomaterials (Basel). 2018;8(6). Epub 20180603. doi: 10.3390/nano8060401. PubMed PMID: 29865277; PubMed Central PMCID: PMCPMC6027353.
112. Chicheł A, Skowronek J, Kubaszewska M, Kanikowski M. Hyperthermia – description of a method and a review of clinical applications. Reports of Practical Oncology & Radiotherapy. 2007;12(5):267-75. doi: https://doi.org/10.1016/S1507-1367(10)60065-X.
113. Kaur P, Hurwitz MD, Krishnan S, Asea A. Combined hyperthermia and radiotherapy for the treatment of cancer. Cancers (Basel). 2011;3(4):3799-823. Epub 20110930. doi: 10.3390/cancers3043799. PubMed PMID: 24213112; PubMed Central PMCID: PMCPMC3763397.
114. Ohguri T, Imada H, Yahara K, Moon SD, Yamaguchi S, Yatera K, et al. Re-irradiation plus regional hyperthermia for recurrent non-small cell lung cancer: a potential modality for inducing long-term survival in selected patients. Lung Cancer. 2012;77(1):140-5. Epub 20120323. doi: 10.1016/j.lungcan.2012.02.018. PubMed PMID: 22445656.
115. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. Adv Drug Deliv Rev. 2013;65(13-14):1866-79. Epub 20131010. doi: 10.1016/j.addr.2013.09.019. PubMed PMID: 24120656; PubMed Central PMCID: PMCPMC5812459.
116. Amreddy N, Babu A, Panneerselvam J, Srivastava A, Muralidharan R, Chen A, et al. Chemo-biologic combinatorial drug delivery using folate receptor-targeted dendrimer nanoparticles for lung cancer treatment. Nanomedicine. 2018;14(2):373-84. Epub 20171116. doi: 10.1016/j.nano.2017.11.010. PubMed PMID: 29155362; PubMed Central PMCID: PMCPMC5844816.
117. Sharma A, Shambhwani D, Pandey S, Singh J, Lalhlenmawia H, Kumarasamy M, et al. Advances in Lung Cancer Treatment Using Nanomedicines. ACS Omega. 2023;8(1):10-41. Epub 20221229. doi: 10.1021/acsomega.2c04078. PubMed PMID: 36643475; PubMed Central PMCID: PMCPMC9835549.
118. Koutu V, Gupta M, Das S, Rawat DK, Kharade V, Pasricha RK. Nanotechnology in Lung Cancer Therapeutics: A Narrative Review. Cureus. 2023;15(1):e34245. Epub 20230126. doi: 10.7759/cureus.34245. PubMed PMID: 36855484; PubMed Central PMCID: PMCPMC9968214.
119. Wang W, Hao Y, Liu Y, Li R, Huang DB, Pan YY. Nanomedicine in lung cancer: Current states of overcoming drug resistance and improving cancer immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2021;13(1):e1654. Epub 20200722. doi: 10.1002/wnan.1654. PubMed PMID: 32700465.
120. Carrasco-Esteban E, Domínguez-Rullán JA, Barrionuevo-Castillo P, Pelari-Mici L, Leaman O, Sastre-Gallego S, et al. Current role of nanoparticles in the treatment of lung cancer. J Clin Transl Res. 2021;7(2):140-55. Epub 20210316. PubMed PMID: 34104817; PubMed Central PMCID: PMCPMC8177846.
121. Zhou W, Liu Z, Wang N, Chen X, Sun X, Cheng Y. Hafnium-Based Metal-Organic Framework Nanoparticles as a Radiosensitizer to Improve Radiotherapy Efficacy in Esophageal Cancer. ACS Omega. 2022;7(14):12021-9. Epub 20220330. doi: 10.1021/acsomega.2c00223. PubMed PMID: 35449918; PubMed Central PMCID: PMCPMC9016869.
122. Wang J, Pan J, Tang Y, Chen J, Fei X, Xue W, et al. Advances of hafnium based nanomaterials for cancer theranostics. Front Chem. 2023;11:1283924. Epub 20231124. doi: 10.3389/fchem.2023.1283924. PubMed PMID: 38075497; PubMed Central PMCID: PMCPMC10704140.
123. Lan G, Ni K, Veroneau SS, Song Y, Lin W. Nanoscale Metal-Organic Layers for Radiotherapy-Radiodynamic Therapy. J Am Chem Soc. 2018;140(49):16971-5. Epub 20181128. doi: 10.1021/jacs.8b11593. PubMed PMID: 30485084.
124. Hu Y, Paris S, Bertolet G, Barsoumian HB, Wang Q, Da Silva J, et al. NBTXR3 improves the efficacy of immunoradiotherapy combining nonfucosylated anti-CTLA4 in an anti-PD1 resistant lung cancer model. Front Immunol. 2022;13:1022011. Epub 20221103. doi: 10.3389/fimmu.2022.1022011. PubMed PMID: 36405757; PubMed Central PMCID: PMCPMC9669748.
125. Hu Y, Paris S, Barsoumian H, Abana CO, He K, Wasley M, et al. Radiation Therapy Enhanced by NBTXR3 Nanoparticles Overcomes Anti-PD1 Resistance and Evokes Abscopal Effects. Int J Radiat Oncol Biol Phys. 2021;111(3):647-57. Epub 20210706. doi: 10.1016/j.ijrobp.2021.06.041. PubMed PMID: 34242713.
126. Hu Y, Paris S, Sahoo N, Bertolet G, Wang Q, Wang Q, et al. Nanoparticle-enhanced proton beam immunoradiotherapy drives immune activation and durable tumor rejection. JCI Insight. 2023;8(12). Epub

20230622. doi: 10.1172/jci.insight.167749. PubMed PMID: 37345658; PubMed Central PMCID: PMCPMC10371249.
127. Shen C, Frakes J, Niu J, Weiss J, Caudell J, Seiwert T, et al. 684 NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with advanced cancers: results from an ongoing dose escalation phase I trial (Study 1100). BMJ Specialist Journals; 2022.
128. Ngema LM, Adeyemi SA, Marimuthu T, Choonara YE. A review on engineered magnetic nanoparticles in Non-Small-Cell lung carcinoma targeted therapy. Int J Pharm. 2021;606:120870. Epub 20210708. doi: 10.1016/j.ijpharm.2021.120870. PubMed PMID: 34245844.
129. Mukherjee S, Liang L, Veiseh O. Recent Advancements of Magnetic Nanomaterials in Cancer Therapy. Pharmaceutics. 2020;12(2). Epub 20200211. doi: 10.3390/pharmaceutics12020147. PubMed PMID: 32053995; PubMed Central PMCID: PMCPMC7076668.
130. Li K, Chen B, Xu L, Feng J, Xia G, Cheng J, et al. Reversal of multidrug resistance by cisplatin-loaded magnetic Fe3O4 nanoparticles in A549/DDP lung cancer cells in vitro and in vivo. International Journal of Nanomedicine. 2013:1867-77.
131. Wan X, Song Y, Song N, Li J, Yang L, Li Y, et al. The preliminary study of immune superparamagnetic iron oxide nanoparticles for the detection of lung cancer in magnetic resonance imaging. Carbohydr Res. 2016;419:33-40. Epub 20151112. doi: 10.1016/j.carres.2015.11.003. PubMed PMID: 26649917.
132. Zhao J, Li X, Wang X, Wang X. Fabrication of Hybrid Nanostructures Based on Fe(3)O(4) Nanoclusters as Theranostic Agents for Magnetic Resonance Imaging and Drug Delivery. Nanoscale Res Lett. 2019;14(1):200. Epub 20190607. doi: 10.1186/s11671-019-3026-7. PubMed PMID: 31175468; PubMed Central PMCID: PMCPMC6555842.
133. Revia RA, Zhang M. Magnetite nanoparticles for cancer diagnosis, treatment, and treatment monitoring: recent advances. Materials today. 2016;19(3):157-68.
134. Sadhukha T, Wiedmann TS, Panyam J. Inhalable magnetic nanoparticles for targeted hyperthermia in lung cancer therapy. Biomaterials. 2013;34(21):5163-71.
135. Baskar G, Ravi M, Panda JJ, Khatri A, Dev B, Santosham R, et al. Efficacy of Dipeptide-Coated Magnetic Nanoparticles in Lung Cancer Models Under Pulsed Electromagnetic Field. Cancer Invest. 2017;35(6):431-42. Epub 20170524. doi: 10.1080/07357907.2017.1318894. PubMed PMID: 28537455.
136. Kim SJ, Puranik N, Yadav D, Jin JO, Lee PCW. Lipid Nanocarrier-Based Drug Delivery Systems: Therapeutic Advances in the Treatment of Lung Cancer. Int J Nanomedicine. 2023;18:2659-76. Epub 20230518. doi: 10.2147/ijn.S406415. PubMed PMID: 37223276; PubMed Central PMCID: PMCPMC10202211.
137. Dristant U, Mukherjee K, Saha S, Maity D. An Overview of Polymeric Nanoparticles-Based Drug Delivery System in Cancer Treatment. Technol Cancer Res Treat. 2023;22:15330338231152083. doi: 10.1177/15330338231152083. PubMed PMID: 36718541; PubMed Central PMCID: PMCPMC9893377.
138. Wang T, Suita Y, Miriyala S, Dean J, Tapinos N, Shen J. Advances in Lipid-Based Nanoparticles for Cancer Chemoimmunotherapy. Pharmaceutics. 2021;13(4). Epub 20210409. doi: 10.3390/pharmaceutics13040520. PubMed PMID: 33918635; PubMed Central PMCID: PMCPMC8069739.
139. Mair A, Nocera F, Wolf D, Pircher A. Lipid nanoparticles in the treatment of lung cancer—hype or hope? memo - Magazine of European Medical Oncology. 2023;16(3):193-7. doi: 10.1007/s12254-023-00904-2.
140. Mao K, Zhang W, Yu L, Yu Y, Liu H, Zhang X. Transferrin-Decorated Protein-Lipid Hybrid Nanoparticle Efficiently Delivers Cisplatin and Docetaxel for Targeted Lung Cancer Treatment. Drug Des Devel Ther. 2021;15:3475-86. Epub 20210810. doi: 10.2147/dddt.S296253. PubMed PMID: 34413632; PubMed Central PMCID: PMCPMC8369919.
141. Wu C, Xu J, Hao Y, Zhao Y, Qiu Y, Jiang J, et al. Application of a lipid-coated hollow calcium phosphate nanoparticle in synergistic co-delivery of doxorubicin and paclitaxel for the treatment of human lung cancer A549 cells. Int J Nanomedicine. 2017;12:7979-92. Epub 20171031. doi: 10.2147/ijn.S140957. PubMed PMID: 29184399; PubMed Central PMCID: PMCPMC5673048.
142. Yang Y, Huang Z, Li J, Mo Z, Huang Y, Ma C, et al. PLGA Porous Microspheres Dry Powders for Codelivery of Afatinib-Loaded Solid Lipid Nanoparticles and Paclitaxel: Novel Therapy for EGFR Tyrosine Kinase Inhibitors Resistant Nonsmall Cell Lung Cancer. Adv Healthc Mater. 2019;8(23):e1900965. Epub 20191030. doi: 10.1002/adhm.201900965. PubMed PMID: 31664795.
143. Nakamura T, Sato T, Endo R, Sasaki S, Takahashi N, Sato Y, et al. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation. J Immunother Cancer. 2021;9(7). doi: 10.1136/jitc-2021-002852. PubMed PMID: 34215690; PubMed Central PMCID: PMCPMC8256839.
144. Amreddy N, Babu A, Muralidharan R, Munshi A, Ramesh R. Polymeric Nanoparticle-Mediated Gene Delivery for Lung Cancer Treatment. Top Curr Chem (Cham). 2017;375(2):35. Epub 20170313. doi: 10.1007/s41061-017-0128-5. PubMed PMID: 28290155; PubMed Central PMCID: PMCPMC5480422.
145. Zhang Y, Huang Y, Li S. Polymeric micelles: nanocarriers for cancer-targeted drug delivery. AAPS PharmSciTech. 2014;15(4):862-71. Epub 20140404. doi: 10.1208/s12249-014-0113-z. PubMed PMID: 24700296; PubMed Central PMCID: PMCPMC4113619.

146. Ezhilarasan D, Lakshmi T, Mallineni SK. Nano-based targeted drug delivery for lung cancer: therapeutic avenues and challenges. Nanomedicine (Lond). 2022;17(24):1855-69. Epub 20220321. doi: 10.2217/nnm-2021-0364. PubMed PMID: 35311343.
147. Chen G, Zhang Y, Deng H, Tang Z, Mao J, Wang L. Pursuing for the better lung cancer therapy effect: Comparison of two different kinds of hyaluronic acid and nitroimidazole co-decorated nanomedicines. Biomed Pharmacother. 2020;125:109988. Epub 20200212. doi: 10.1016/j.biopha.2020.109988. PubMed PMID: 32059173.
148. Zhao Y, Liu K, Li J, Liao J, Ma L. Engineering of hybrid anticancer drug-loaded polymeric nanoparticles delivery system for the treatment and care of lung cancer therapy. Drug Deliv. 2021;28(1):1539-47. doi: 10.1080/10717544.2021.1934187. PubMed PMID: 34282705; PubMed Central PMCID: PMCPMC8293970.
149. Shukla SK, Kulkarni NS, Farrales P, Kanabar DD, Parvathaneni V, Kunda NK, et al. Sorafenib Loaded Inhalable Polymeric Nanocarriers against Non-Small Cell Lung Cancer. Pharm Res. 2020;37(3):67. Epub 20200312. doi: 10.1007/s11095-020-02790-3. PubMed PMID: 32166411.
150. Han J, Yang W, Li Y, Li J, Jiang F, Xie J, et al. Combining Doxorubicin-Conjugated Polymeric Nanoparticles and 5-Aminolevulinic Acid for Enhancing Radiotherapy against Lung Cancer. Bioconjug Chem. 2022;33(4):654-65. Epub 20220406. doi: 10.1021/acs.bioconjchem.2c00066. PubMed PMID: 35385661.
151. Menon JU, Kuriakose A, Iyer R, Hernandez E, Gandee L, Zhang S, et al. Dual-Drug Containing Core-Shell Nanoparticles for Lung Cancer Therapy. Sci Rep. 2017;7(1):13249. Epub 20171016. doi: 10.1038/s41598-017-13320-4. PubMed PMID: 29038584; PubMed Central PMCID: PMCPMC5643549.