REVIEW

Lib Oncol. 2025;53(2-3):147–151

doi: 10.20471/LO.2025.53.02-03.15

Re-irradiation of locoregional recurrence of lung cancer using conventional radiotherapy techniques

Lana Ljubičić, Dora Gudelj, Dora Radoš, Lea Galunić Bilić

Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia

Summary

Advancements in diagnostic modalities, surgical techniques, systemic therapies, and radiotherapy have significantly improved the survival rates among patients with lung cancer. Consequently, the need for re-irradiation has increased in cases of locoregional recurrence or development of a new primary tumor. Re-irradiation can achieve locoregional disease control and may potentially extend survival while maintaining an acceptable toxicity profile.

Critical factors influencing the decision to perform re-irradiation include previous radiation dose, the interval between treatment cycles, and the cumulative doses to organs at risk. Normal tissue tolerance limits total dose, requiring minimized exposure to lungs, heart, esophagus, major vessels, bronchi, and brachial plexus.

The objective of this paper is to evaluate the clinical outcomes and toxicity associated with conventional re-irradiation techniques in patients with locally recurrent lung cancer through systemic literature review. In the absence of standardized treatment guidelines, systematic collection and analysis of clinical data are essential to develop safe and effective re-irradiation protocols, particularly in patients with limited tumor burden and good performance status.

KEYWORDS: *conventional radiotherapy, re-irradiation toxicity, radiobiology, dose constraints, locoregional recurrence*

INTRODUCTION

Advancements in diagnostics, surgical treatment, the development of antitumor drugs, and radiotherapy techniques have led to prolonged survival rates in patients with lung cancer. As survival improves, isolated recurrences or new primary tumors occur more frequently, increasing the need for re-irradiation. Re-irradiation plays a key role in achieving local disease control and potentially extending survival, while aiming to maintain low toxicity levels. Although literature data are limited, the decision to perform re-irradiation must take into account a number of factors: previous radiotherapy dose, volume, and location of the irradiated area, field overlap, additional therapies, time elapsed since initial treatment, and characteristics of the affected tissue. The purpose of the intervention – whether radical or palliative – further guides the therapeutic approach. Although modern methods such as stereotactic ablative radiotherapy and proton therapy offer greater precision and lower the risk of toxicity, in many countries conventional techniques like intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are most commonly used. A multidisciplinary approach and thorough risk-benefit assessment are essential in making an optimal treatment decision. This paper aims to examine treatment outcomes and toxicity related to the use of conventional re-irradiation techniques in the locoregional recurrence of lung cancer(1-5).

Corresponding author: *Lana Ljubičić, Department of Oncology, University Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia. e-mail: dr.lana.ljubicic@gmail.com*

RADIOBIOLOGY OF RE-IRRADIATION IN LUNG CANCER

Re-irradiation of the lungs is defined as any radiation dose delivered after the initial radical radiotherapy to the thorax, with overlap of the previous dose in the planned target volume (PTV) or organs at risk. It may be used in cases of local recurrence, metachronous lung tumors distant from the original primary tumor, new tumors of different histology, or metastatic lesions within the previous radiation field. The re-irradiation approach depends on the tumor's biological characteristics, expected outcomes, potential toxicity, and the patient's overall condition.

In patients treated with curative intent, the median overall survival is approximately 17 months, while a small number of selected patients with small recurrent tumors may achieve long-term survival of 20 months or more. A 2021 analysis showed an increase in the number of patients receiving more than five fractions of radiotherapy from 0.9% in 2011 to 6.5% in 2019,confirming the growing role of re-irradiation in modern oncology practice.

The radiobiology of lung cancer re-irradiation is based on assessing the ability of healthy tissue to recover between two radiation courses, with emphasis on the remaining tolerance capacity of tissue to additional doses of ionizing radiation. This capacity depends on tissue type and the time interval between treatments. For quantifying and comparing doses, equivalent dose in 2 Gy fractions (EQD2) and biologically effective dose (BED) are used, with re-irradiation often aiming for higher BED due to insufficient disease control after initial therapy. Although the initial radiotherapy plan often limits the possibility of re-radiation, a longer interval between treatments can increase the safety of retreatment. In a systematic review of 1,243 patients, the median time between radiation courses was 18 months, while a minimum interval of 6 months is considered acceptable in clinical practice(1,3,6).

The lungs, as an organ with low regenerative capacity and an α/β ratio of approximately 3 Gy, are particularly sensitive to radiation. They tolerate a median dose of 18 to 20 Gy, and exceeding this dose can lead to irreversible damage to alveoli, bronchi, and vascular structures, impairing gas exchange. Early side effects may be reversible, whereas late effects, such as pulmonary fibrosis, are permanent and potentially progressive.

New biomarkers, such as microRNAs (miRNAs), are promising in predicting late tissue injuries. Animal studies indicate a correlation between changes in miRNA levels and the development of pulmonary fibrosis, pneumonitis, and cardiac complications – opening possibilities for earlier detection and a personalized approach to re-irradiation(6,7,8).

POTENTIAL TOXICITY IN THORACIC RE-IRRADIATION

With the use of older, 2D radiotherapy techniques, thoracic re-irradiation was associated with up to 14% potentially fatal (grade 5) toxicity, which led to the use of lower radiation doses. Technological advancements have reduced complication rates, yet the risk of toxicity remains due to the cumulative dose on organs at risk(9).

Pneumonitis and fibrosis

Radiation pneumonitis, which may progress to fibrosis, occurs in 5% to 23% of patients, depending on the volume of irradiated lung tissue and the dose administered. According to RTOG guidelines, the recommended volume of normal lung tissue receiving a radiation dose of at least 20 Gy (V20) should be below 37%, with a mean lung dose (MLD) of less than 20 Gy. A 2018 study by Ren et al. identified that overlapping radiation plans are predictors of ≥ grade 3 pneumonitis.

Pulmonary toxicity after re-irradiation is influenced by inflammatory processes triggered by endothelial cell death, inflammatory cytokines, and the production of reactive oxygen species. Transforming growth factor-beta (TGF-β) plays a key role in the development of fibrosis. Cumulative doses exceeding recommended thresholds can lead to irreversible impairment of lung function. Suggested cumulative dose limits include: Dmean < 22 Gy (EQD2 after 9 months), V20 < 40% (EQD2). For the trachea/proximal bronchial tree, Dmax < 110 Gy(9,10,11).

Cardiotoxicity

The heart is one of the most radiosensitive organs due to potential complications such as cardiomyopathy, pericarditis, and coronary artery disease. Recommended dose constraints for the heart include a mean dose below 15 Gy, volume that receives 30 Gy (V30) under 46%, V45 under

66.7%, and V60 under 33%. At higher doses, pericarditis is a common complication, while extremely high cumulative doses (>120 Gy) can lead to fatal complications such as aortic rupture. Recommended cumulative dose constraints: Dmean < 70 Gy (EQD2 after 9 months); V40 < 50% (EQD2). For the aorta and great vessels: Dmax < 120 Gy(10,11).

Esophagitis

Esophagitis occurs with doses exceeding 58 Gy and mean doses above 34 Gy, particularly when combined with concurrent chemotherapy. Acute esophagitis, which typically resolves spontaneously within 4 – 6 weeks after radiotherapy, presents as dysphagia and is characterized by inflammatory changes of the mucosa, with or without ulceration. Late esophagitis can appear months or even years after treatment and is usually the result of fibrosis or esophageal strictures. Recommended cumulative EQD2 doses for the esophagus range from 75 Gy to 100 Gy, with a V55 constraint of less than 35%(10,13).

Spinal Cord

With conventional fractionation of 2 Gy per day, including the full cross-section of the spinal cord, total radiotherapy doses of 50 Gy, 60 Gy, and 70 Gy are associated with a 0.2%, 6%, and 50% risk of myelopathy, respectively. Re-irradiation data from both animal and human studies suggest that partial repair of radiation-induced subclinical damage becomes apparent around 6 months after radiotherapy and continues to improve over the following 2 years. The maximum cumulative EQD2 for the spinal cord is 67.5 Gy, provided that the initial dose did not exceed 50 Gy(12).

Secondary Neoplasms

Secondary neoplasms may develop between 5 and 20 years after radiation therapy. The most commonly observed are sarcomas, breast cancer, and lung cancer, although esophageal carcinomas and pleural mesotheliomas have also been reported(10-12).

RE-IRRADIATION USING CONVENTIONAL RADIATION TECHNIQUES

Reirradiation using conventional radiation techniques represents an important therapeutic option for locally recurrent lung cancer, especially in patients with smaller tumor volumes and limited involvement of mediastinal lymph nodes. The improvement of systemic therapies has extended the overall survival of patients; however, the importance of locoregional disease control is increasingly recognized as a significant factor influencing treatment outcomes(13). A study by Machtay et al. demonstrated that every 1 Gy increase in biologically effective dose in patients with advanced non-small cell lung cancer (NSCLC) was associated with a 4% relative improvement in survival following radical radiotherapy(14).

Early reirradiation studies using 2D and 3D conformal techniques with palliative doses up to 30 Gy showed limited results, with median survival lasting only a few months. The introduction of intensity-modulated radiotherapy (IMRT) enabled better dose distribution and sparing of normal tissue, improving treatment outcomes(14). Kruser et al. reported a median survival of 5.1 months for NSCLC and 3.1 months for small-cell lung cancer (SCLC) after IMRT re-irradiation(15). Schlampp et al. observed a median overall survival of 9.3 months and local progression-free survival of 6.5 months using conventional techniques(13).

Gullhaug et al. confirmed that combining Three-Dimensional Conformal Radiation Therapy (3D-CRT) with IMRT/SBRT techniques results in better outcomes, including a 79% three-month survival rate. Grambozov et al. reported a median overall survival of 18.4 months after high-dose re-irradiation with IMRT/VMAT, with smaller tumor volume correlating with longer survival(16,17).

In summary, conventional radiation techniques, especially when combined with modern modalities, provide significant local control and survival benefits with acceptable toxicity in carefully selected patients. Further research is necessary to optimize dose limits, indications, and safety protocols.

CONCLUSION

While re-irradiation remains a complex clinical challenge due to cumulative dose limitations and potential toxicity to organs at risk, emerging evidence suggests that, when carefully planned, it can achieve meaningful local control and prolong survival. Lung and heart dose constraints must be

strictly adhered to, and treatment decisions should be made within a multidisciplinary team based on individualized risk-benefit assessments. The decision requires careful evaluation of radiobiological parameters, cumulative doses to organs at risk, and the patient's overall condition. Radiobiological models, biomarkers such as microRNAs, and increasing clinical data contribute to a better understanding of the safety limits of re-irradiation. Although favorable outcomes have been achieved in selected patients, especially those with smaller tumor volumes and good functional status, further prospective studies are needed to more precisely define the indications, optimal doses, and long-term effects of re-irradiation in lung cancer.

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Sažetak

Reiradijacija lokoregionalnog povrata karcinoma pluća konvencionalnim tehnikama zračenja

L. Ljubičić, D. Gudelj, D. Radoš, L. Galunić Bilić

Napretkom u dijagnostičkim, kirurškim i radioterapijskim tehnikama te sustavnoj terapiji, postignuto je dulje preživljenja bolesnika s karcinomom pluća, čime raste potreba za reiradijacijom u slučajevima lokalnog recidiva ili novih primarnih tumora. Reiradijacija omogućuje lokoregionalnu kontrolu bolesti i potencijalno produljuje preživljenje, uz nužnost održavanja niske toksičnosti. Ključni čimbenici u odlučivanju o ponovnom zračenju uključuju prethodnu dozu, interval između zračenja te kumulativne doze na rizične organe. Budući da tolerancija zdravih tkiva ograničava dozu, posebna pažnja posvećuje se zaštiti pluća, srca, jednjaka, krvnih žila, bronha i brahijalnog spleta.

Cilj ovog rada je, kroz proučavanje stručne literature, analizirati ishode i toksičnosti konvencionalnih tehnika reiradijacije kod lokalnog recidiva raka pluća. U nedostatku standardiziranih smjernica, nužno je sustavno prikupljanje i analiza kliničkih podataka radi oblikovanja sigurnih i učinkovitih protokola za reiradijaciju povrata raka pluća, posebno kod bolesnika s manjim tumorima i dobrim općim stanjem.

KLJUČNE RIJEČI: *konvencionalna radioterapija, toksičnost reiradijacije, radiobiologija, ograničenja doze, lokoregionalni povrat*