CASE REPORT

# Revisiting the Role of Adjuvant Radiotherapy in Non-Small Cell Lung Cancer

## *Revisitar o Papel da Radioterapia Adjuvante Cancro do Pulmão de Não Pequenas Células*

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The role of adjuvant radiotherapy in the management of non–small cell lung cancer (NSCLC) has been a subject of considerable debate over the past decades. Despite significant advances in systemic therapies and surgical techniques, the utility of postoperative radiotherapy (PORT) remains controversial in thoracic oncology. A thorough analysis of historical data, recent clinical trials, and emerging therapeutic approaches is essential to comprehend the present perspective and future direction of PORT in NSCLC. The skepticism surrounding PORT originated from a pivotal meta-analysis published in 1998 by the PORT Meta-analysis Trialists Group.[1] This study reviewed data from nine heterogeneous randomized controlled trials involving patients who received PORT after complete surgical resection of NSCLC. The meta-analysis found that, although PORT improved local

control by approximately 20%, it was associated with a detrimental effect on overall survival, particularly in patients with early-stage disease (pN0 and pN1). There was an absolute 7% increase in two-year mortality among patients who received PORT compared to those who did not. Importantly, the survival difference was not statistically significant in patients with mediastinal lymph node involvement (pN2).[1] Several limitations of this meta-analysis become apparent when considered in the context of modern clinical practices. The included trials were conducted between the 1960s and early 1990s — a period characterized by inadequate staging techniques, absence of positron emission tomography-computed tomography (PET-CT) imaging, and lack of standardized adjuvant chemotherapy protocols. Additionally, the radiotherapy technology of that era was less precise, often utilizing cobalt-60 units and non-conformal techniques, leading to higher doses to surrounding healthy tissues and increased toxicity.[1] In subsequent decades, significant advances in radiotherapy techniques —such as three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) and image-guided treatments — have improved the precision of radiation delivery, more effectively sparing normal tissues. These improvements prompted reevaluations of the role of PORT in NSCLC. Retrospective analyses and clinical studies indicated potential benefits of PORT in patients with mediastinal lymph node involvement (pN2 disease). For instance, the ANITA trial, a randomized study evaluating adjuvant vinorelbine and cisplatin chemotherapy, suggested that PORT improved survival in patients with pN2 disease who also received adjuvant chemotherapy.[2] However, these findings were not from prospective, randomized comparisons specific to PORT and were subject to inherent biases. The absence of high-quality randomized controlled trials specifically designed to evaluate PORT in the modern era was addressed by two significant trials: the European LungART trial and the Chinese PORT-C trial. The LungART trial included 501 patients with completely resected stage IIIA N2 NSCLC who had received mostly adjuvant chemotherapy.[3] Participants were randomized to receive PORT, administered at a dose of 54 Gy using 3D-CRT or IMRT, or no further treatment. The primary endpoint was disease-free survival (DFS). The results showed that while PORT significantly reduced mediastinal recurrence rates — from 46% in the control group to 25% in the PORT group — it did not provide a statistically significant improvement in DFS or overall survival (OS). Five-year DFS rates were 47.1% in the PORT arm versus 43.8% in the control arm. Additionally, there was an increase in cardiopulmonary toxicity in the PORT group.[3] A crucial aspect of the LungART trial was the central pathological review of surgical specimens. Nevertheless, a subset analysis found that only 29% of cases achieved complete (R0) resections according to the International Association for the Study of Lung Cancer (IASLC); 30% were reclassified as having microscopic residual disease (R1), and 41% were deemed uncertain.[4] This finding raises concerns about the completeness of surgical resections and suggests that the potential benefits of PORT might have been diminished by suboptimal surgical outcomes. Furthermore, a significant proportion of patients had multi-level N2 disease, with 24% involving multiple mediastinal lymph node stations, prompting the question of whether these patients might have been better managed with definitive chemoradiotherapy instead of surgery. The Chinese PORT-C trial included 394 patients with pathologic stage IIIA N2 NSCLC.5 Similar to LungART, patients were randomized to receive PORT at a dose of 50 Gy in 25 fractions or observation after surgery and adjuvant chemotherapy. The trial found that PORT reduced loco-regional recurrence rates — from 33.6% in the observation group to 19.9% in the PORT group — but did not significantly improve DFS or OS.[5] Notably, the incidence of cardiopulmonary toxicity was lower in the PORT-C trial compared to LungART, possibly due to the higher use of IMRT (89% in PORT-C versus 11% in LungART), known to reduce radiation exposure to normal tissues.[6] These trials collectively suggest that, although PORT improves local control by reducing mediastinal recurrences, it does not translate into improved survival outcomes and is associated with increased toxicity. This lack of survival benefit questions the routine use of PORT in patients with completely resected pN2 NSCLC. Several considerations emerge from these findings. First, the limited use of advanced radiotherapy techniques like IMRT in LungART may have contributed to higher toxicity and absence of survival benefit. Modern radiotherapy modalities offer better dose conformity and sparing of critical structures, potentially mitigating adverse effects. Second, patient heterogeneity and the extent of mediastinal involvement may influence PORT's efficacy. Subgroup analyses suggest that patients with a higher burden of mediastinal disease might benefit more from PORT. Additionally, patients with extracapsular extension of lymph node metastases or incomplete resections (R1) may represent subgroups where PORT could be advantageous.[7] Current clinical guidelines reflect the evolving understanding of PORT's role. The American Society of Clinical Oncology (ASCO), informed by preliminary results

from LungART, recommends against the routine use of PORT in patients without residual disease following complete resection.[8] The National Comprehensive Cancer Network (NCCN) suggests that PORT may be considered for patients with high-risk features but acknowledges the lack of clear evidence to support its routine use.[9] Identifying patients who may benefit from PORT remains a challenge. Potential high-risk factors include significant mediastinal tumor burden, extracapsular extension, specific histological subtypes, and persistent pN2 disease after neoadjuvant therapy. The LungART trial indicated that the involvement of two or more N2 stations might serve as a threshold for considering PORT.[3]

The advent of novel perioperative systemic therapies, particularly immunotherapies, has further complicated the landscape. Trials such as CheckMate 816 have demonstrated significant benefits of neoadjuvant immunotherapy in resectable NSCLC, including increased pathological complete response rates and improved DFS.[10] These advances raise new questions about the role of PORT in the context of improved systemic control. Effective systemic therapies may reduce the impact of local recurrences on overall outcomes. Conversely, as distant control improves, local failures might become a more significant contributor to disease progression, potentially enhancing the importance of local control measures like PORT. Integrating radiotherapy with immunotherapy offers intriguing possibilities. The synergistic effects observed suggest that combining PORT with immunotherapy could potentiate systemic anti-tumor responses.[11] Radiotherapy can modulate the tumor microenvironment and stimulate immune responses. However, this approach raises concerns about increased toxicity, particularly pneumonitis, necessitating careful evaluation in clinical trials. In the targeted therapy space, ADAURA (osimertinib) and ALINA (alectinib) trials demonstrate strong systemic control, making the role of PORT even less relevant for patients with driver mutations.

An underexplored area is the management of patients who receive neoadjuvant therapies but are not surgical candidates due to disease progression. The role of definitive radiotherapy in this context remains undefined, highlighting a gap in current literature and clinical practice. Additionally, using circulating tumor DNA (ctDNA) as a biomarker for minimal residual disease may help identify patients at higher risk of recurrence who could benefit from PORT.[11] This biomarker-driven approach could facilitate personalized treatment strategies, optimizing the balance between efficacy and toxicity. Despite the evolving therapeutic landscape, radiation oncologists often remain underrepresented in guideline panels and multidisciplinary discussions. This underrepresentation highlights the need for greater inclusion of radiation oncology expertise in developing comprehensive treatment guidelines and emphasizes the importance of multidisciplinary collaboration in optimizing patient outcomes. Looking ahead, several avenues exist for refining the role of PORT in NSCLC. Advanced radiotherapy techniques offer the potential for improved targeting and reduced toxicity. Proton therapy can spare normal tissues more effectively, potentially reducing cardiopulmonary toxicity.[6] The application of artificial intelligence in treatment planning may further personalize therapy, optimizing the therapeutic ratio. Addressing cardiotoxicity remains critical, particularly given the increased incidence observed in trials like LungART and RTOG 0617. Strategies to mitigate cardiotoxicity include refining dose constraints for cardiac structures and integrating cardioprotective interventions.[6] Clinical trials are essential to clarify PORT's role amidst evolving systemic therapies. Prospective studies focusing on high-risk populations and incorporating modern radiotherapy techniques are needed. Translational research investigating the biological mechanisms underlying radiation response can inform combination strategies with immunotherapies. In conclusion, while the routine use of classic PORT in NSCLC is declining, radiotherapy may still play a role in carefully selected patients. Identifying high-risk individuals who might benefit from PORT requires a personalized approach, incorporating clinical, pathological, and molecular factors. Patients with high-risk features, such as R1 resections, multiple N2 station involvement or extracapsular extension may still derive benefit, whereas those achieving complete resection with modern systemic therapies likely do not. The role of PORT in the era of neoadjuvant immunotherapy remains an open question. Future research should aim to elucidate PORT's role in the context of modern systemic therapies, emphasizing personalized medicine and technological innovation.

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