Postoperative Radiation Therapy Should Not Be Used for the Therapy of Stage III-N2 NSCLC

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Surgery has been the treatment of choice for fit patients with stage I to IIIA NSCLC, but after complete resection of resectable NSCLC, patients are still at high risk of local and distant recurrence. This has resulted in a move toward a multimodality treatment approach being increasingly adopted in the past two decades. Adjuvant platinum-based chemotherapy is associated with an absolute survival benefit of approximately 5% at 5 years and has become the standard of care in patients with completely resected stage II to IIIA NSCLC.1 More recently, studies have focused on the use of targeted treatments and immunotherapy in this setting and are starting to report promising results.

Another strategy to improve outcome, aimed at reducing the risk of local recurrence, is the use of postoperative radiotherapy (PORT). PORT was evaluated in several randomized controlled trials (RCTs) performed in the 1980 to 1990s, and data from nine of these studies were pooled in a meta-analysis published in 1998, revealing poorer outcomes for pN0 and pN1 diseases.2 It was hypothesized that the poorer survival in patients receiving PORT could be related to the toxicity of thoracic radiotherapy, particularly because suboptimal radiotherapy techniques by today’s standards were used. This hypothesis was subsequently supported by an increasing body of evidence from randomized and prospective studies that reveal, in addition to the recognized pulmonary toxicities, a clear association between radiation dose delivered to the heart and survival.3 Nevertheless, the 1998 meta-analysis revealed no clear evidence of an adverse effect of PORT in patients with mediastinal nodal involvement, that is, stage III-N2. This left the question open in this subgroup and warranted further studies in the era of modern oncologic management.

Because the publication of the PORT meta-analysis, there have been significant improvements in supportive care, surgical techniques, and in selection of patients with 18F-fluorodeoxyglucose positron emission tomography computed tomography scans and brain imaging leading to improved outcomes. Alongside this, there have been developments in radiotherapy techniques, allowing radiation oncologists to take a more conformal approach to radiotherapy planning and delivery which could improve the outcome of PORT by decreasing the dose delivered to normal tissues, including the lungs and heart. The hope is that technological improvements in radiotherapy treatments will lead to a decrease in the risk of death from radiotherapy-induced toxicity. This assumption is supported by a further meta-analysis evaluating the role of linear accelerators revealing modern PORT may decrease local relapse and increase overall survival (OS) in stage IIIA-N2 NSCLC.4

Other favorable evidence for PORT comes from studies using the large U.S. national databases and a subgroup analysis of the ANITA trial.5,6 Nevertheless, the increasing concerns regarding the toxicity meant that the role of PORT in patients with completely resected N2 in the era of conformal radiotherapy remained controversial, and the routine use of PORT was debated for each individual patient in multidisciplinary boards on the basis of the evaluation of risks of locoregional relapse.

The LungART RCT was developed in the early 2000s by a multidisciplinary and international team to address
the question of the role of PORT in stage III N2 NSCLC with updated staging, systemic treatment, and surgical and radiotherapy techniques. Over a 10-year period, 501 patients, with PS 0 to 2 and proven N2 disease, were randomized after surgery (± chemotherapy) between PORT or no PORT. Modern staging was used, and 91% of the patients had a positron emission tomography–computed tomography scan with 95% receiving neoadjuvant chemotherapy. All patients were treated with three-dimensional-conformal radiotherapy, but only 11% received intensity-modulated radiotherapy. A significant reduction in mediastinal relapse was reported (25% with PORT and 46% without PORT), but this did not translate into a significant difference in the primary end point of disease-free survival (DFS) (hazard ratio = 0.85 [95% confidence interval: 0.67–1.07]; \( p = 0.16 \)). Similarly, no significant difference was reported in OS (3-year OS 66.5% with PORT versus 68.5% with no PORT). It is important to note that both DFS and OS figures are better than expected in both arms probably owing to the use of modern staging and treatments. A key finding of the study is the significant increase in early and late grades 3 to 5 cardiopulmonary toxicity with the delivery of PORT (7% and 20% in PORT versus 3.2% and 7.7% with no PORT, respectively). Patients in the study underwent pre- and postradiotherapy echocardiograms, which may shed further light on the impact of the thoracic radiotherapy on cardiac toxicity.

Three other RCTs comparing PORT (2 with concurrent chemotherapy) with no PORT were published between 2014 and 2021.6–10 One study closed early owing to poor accrual, and therefore robust conclusions on the impact of PORT on outcomes cannot be made.8 It should be noted that the study populations in the other two studies are different, with one recruiting patients with unsuspected N2 disease and the other with patients with pIIIA-N2 NSCLC after complete resection. The latter study (PORT-C) included 394 patients with 89% of the patients allocated to the PORT arm treated with IMRT.10 This resulted in less than 1% of patients developing grade 3 pneumonitis and none developing grade 3 radiation esophagitis or radiotherapy-related grade 4 or 5 adverse events. Neither study revealed a significant improvement in DFS or OS.9,10

Therefore, the survival evidence from the RCTs does not support a role for the routine use of PORT in patients with stage III-N2 NSCLC. Indeed, the data from the LungART trial revealed an increased risk of cardiopulmonary deaths after PORT and added to the increasing body of evidence that radiation to the cardiopulmonary system can significantly affect outcomes and lead to worse survivals. A number of clinical trials are ongoing to further our understanding of the underlying mechanisms of radiation-induced cardiac toxicity in particular and to evaluate the impact of cardiac avoidance strategies in the radiotherapy planning process.3 Further analyses of the LungART study are awaited and are expected to answer important questions on the quality of surgery. There is increasing recognition that the proposed “R0 (uncertain)” resection margin status—R(un)—is associated with worse prognosis than R0 lung cancer resection,11 particularly for node-positive disease.12 R(un) may be assigned where there are situations that may be associated with microscopic residual disease, such as inadequate intraoperative lymph node dissection, or positivity of the highest lymph node. Uncertainties of completeness of surgical resection may also be present where there are involved lymph nodes that have been removed in fragments or where there is lymph node extracapsular extension of the tumor. The presence of extracapsular extension at the margins of resected lymph nodes should be considered as R1. The further data from LungART will evaluate the impact on adequacies of surgery and certainty of resection margins on the efficacy of PORT. Nevertheless, although such features might be considered to be associated with an increased rate of local recurrence and hence potentially amenable to improve local control with PORT, the evidence from published RCTs is currently lacking.

In conclusion, the survival evidence from the most recent RCTs evaluating the role of PORT does not support its use as a routine treatment for stage III-N2 NSCLC. Nevertheless, these studies have continued to document improvements in local control and there are ongoing improvements in radiotherapy practice with the use of intensity-modulated radiotherapy, volumetric arc therapy, or proton beam therapy that may allow additional reduction in cardiac and pulmonary toxicity of PORT. This means that studies investigating PORT should continue, with precise documentation of the quality of surgery and impact on quality of life. Future studies should also focus on better adjuvant therapies to reduce the risk of disease recurrence, particularly distant metastases that affect approximately 40% of patients as first site of failure.10 Importantly, collection of standard imaging and blood and tissue (e.g., circulating tumor DNA collection for detection of molecular/residual disease) is needed to identify the patients at highest risk of local relapse and death, who would be more likely to see the greatest benefits from adjuvant systemic therapy and/or radiotherapy after surgery.
References


