Postoperative Radiation Therapy Should Be Used for Completely Resected Stage III-N2 NSCLC in Select Patients

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For many years, postoperative radiotherapy (PORT) in completely resected NSCLC with mediastinal involvement (N2) has been a subject of debate. The PORT meta-analysis in 1998 cast doubt on the benefits of PORT, revealing patients with completely resected stage III-N2 NSCLC who receive PORT have no difference in overall survival (OS).1 Nevertheless, recent advancements in radiotherapy techniques led many to question whether modern PORT may improve outcomes.

This was recently addressed by the LUNG-ART trial presented at the European Society of Medical Oncology 2020, which explored the role of modern mediastinal PORT in patients with completely resected stage III-N2 NSCLC.2 It was found that patients who received PORT had no significant difference in 3-year disease-free survival (DFS) or OS compared with patients who did not receive PORT, although there was a 15% absolute benefit in DFS in patients who received PORT. Patients who received PORT had fewer deaths owing to progression and lower mediastinal recurrence, but this was outweighed by an increase in grade 3 to 4 cardiopulmonary toxicities and treatment-related deaths. This trial was criticized for having an excess number of toxicities in the PORT arm because 89% of the patients were treated using a three-dimensional approach, which has been found to be associated with increased cardiac and lung toxicities compared with an intensity-modulated radiation therapy (IMRT) approach based on the Radiation Therapy Oncology Group 0617 secondary analysis.3 It is unclear which patients are at a greater risk of treatment-related deaths, as the full manuscript has not yet been published. Based on the negative results of this trial, the role of PORT for completely resected stage III-N2 NSCLC has been thrown further into doubt.

The PORT-C trial recently published in JAMA Oncology also suggests that PORT may not be beneficial in completely resected stage III-N2 NSCLC.4 In this trial, patients who received PORT had significantly improved local recurrence-free survival, but no improvement in DFS or OS compared with patients who did not receive PORT. Most patients in this trial received PORT using an IMRT approach (89%), which resulted in improved toxicity and fewer treatment-related deaths compared with the LUNG-ART trial. Nevertheless, IMRT did not improve OS because patients who received PORT had a similar number of deaths owing to progression as patients who did not receive PORT.

Despite the results of these two trials, there may be some patients with completely resected stage III-N2 NSCLC who stand to benefit from PORT. In the PORT-C trial mentioned previously, a preplanned exploratory analysis found a significant improvement in DFS with PORT in patients with more than or equal to four lymph nodes compared with patients with one to three lymph nodes.4 Another study found that PORT in completely resected stage III-N2 NSCLC improved DFS in patients with multiple N2 station metastases compared with single N2 station metastases (5-y DFS 41% versus 6%).5 There is also evidence to support the idea of PORT being used for persistent N2 disease after induction chemotherapy. On the basis of multiple studies, patients with

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Persistent N2 disease after induction chemotherapy are at a higher risk of developing distant metastasis and may therefore benefit from further consolidative therapies, such as PORT.6,7 The Swiss Group for Clinical Cancer Research also revealed that persistent N2 disease after induction chemotherapy was associated with worse OS compared with nodal downstaging to N0 to N1 after induction chemotherapy (median OS = 17 mo versus not reached), which suggests a possible role for further consolidative therapies, such as PORT.8 Although there have not been any randomized clinical trials evaluating PORT in the setting of persistent N2 after induction chemotherapy, it may be worth considering given the overall poor outcomes associated with this finding.

Furthermore, molecular markers may play a role in selecting appropriate patients for PORT. For example, PORT may not be beneficial in patients with completely resected stage III-N2 NSCLC with actionable mutations, such as EGFR, wherein EGFR tyrosine kinase inhibitors are indicated. The ADAURA trial found that the use of osimertinib after surgery significantly improved DFS in patients with EGFR-mutated completely resected stage IB to III NSCLC compared with placebo (median DFS not reached versus 27.5 mo).9 Given the efficacy of targeted therapies such as osimertinib after surgery in EGFR-mutated stage III-N2 NSCLC, the relative benefit of PORT may be lower. In contrast, for patients with no actionable mutation who have more limited and less effective systemic options, it may be more imperative to be aggressive with local therapy. In addition, the role of PORT in patients with extracapsular extension (ECE) is unclear. A retrospective review by Vanderbilt University found that positive ECE in completely resected stage III-N2 NSCLC was associated with lower local recurrence-free survival.10 This would suggest a role for consolidative therapies, such as PORT.

Counterintuitively, the study found that PORT was not associated with a higher OS rate in patients with positive ECE but was associated with a higher OS rate in patients with negative ECE. The role for PORT in completely resected stage III-N2 NSCLC with positive ECE warrants further study. A summary of clinical findings and whether or not PORT is indicated is summarized in Table 1.

Given the growing body of literature questioning the benefit of PORT, we acknowledge that the role of PORT in patients with completely resected stage III-N2 NSCLC is rightfully in question. The eventual introduction of immunotherapy into the postoperative setting may further obscure the role for PORT in completely resected stage III-N2 NSCLC. Despite this, we do believe that there should still be a role for PORT in select patients with high-risk features, such as more than or equal to four lymph nodes, multiple N2 stations, and persistent N2 disease after induction chemotherapy. PORT may not be beneficial in patients with actionable mutations, such as EGFR, and it is unclear whether PORT may be beneficial in patients with ECE. Despite emerging data from the LUNG-ART and the PORT-C trials, providers should be cautious on completely eliminating a potentially useful consolidative therapy option in high-risk patients with completely resected stage III-N2 NSCLC. Oncology needs to be viewed in an ever more granular way to identify meaningful differences lost in aggregated data.

### Table 1. Summary of Evidence to Support Whether PORT Should Be Considered in Completely Resected Stage III-N2 NSCLC

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>PORT?</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent N2 disease after chemotherapy</td>
<td>Strongly consider</td>
<td>SAKK—Worse OS in patients with persistent N2 disease compared with patients with nodal downstaging to N0-1 after induction chemotherapy, suggesting a role for further consolidative therapies, such as PORT.9</td>
</tr>
<tr>
<td>Extensive mediastinal involvement</td>
<td>Consider</td>
<td>PORT-C—Improved DFS with PORT in patients with ≥4 lymph nodes compared with patients with 1-3 lymph nodes.</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>Unclear</td>
<td>Vanderbilt—ECE is associated with worse LRFS. Counterintuitively, PORT was associated with improved OS in patients with negative ECE but not in patients with positive ECE. This warrants further study.10</td>
</tr>
<tr>
<td>Presence of actionable mutations</td>
<td>Do not offer</td>
<td>ADAURA—Improved DFS with targeted therapies, such as osimertinib after surgery in EGFR-mutated mutated disease. The relative benefit of PORT may be lower and likely should not be offered.9</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; ECE, extracapsular extension; SAKK, Swiss Group for Clinical Cancer Research; LRFS, local recurrence-free survival; OS, overall survival; PORT, postoperative radiotherapy.

**CRediT Authorship Contribution**

**Jason Liu:** Conceptualization, Data curation, Writing—original draft, Visualization.

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References


