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# Exploring the past, present, and future of postoperative radiotherapy for N2 stage non-small cell lung cancer

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Despite conventionally applied postoperative radiotherapy (PORT) in pathological N2 (pN2) stage non-small cell lung cancer (NSCLC) considering high locoregional recurrence, its survival benefit has been a continuous topic of debate. Although several randomized clinical trials have been conducted, many of them have been withdrawn or analyzed without statistical significance due to slow accrual, making it difficult to determine the efficacy of PORT. Recently, the results of large-scale randomized clinical trials have been published, which showed some improvement in disease-free survival with PORT, but finally had no impact on overall survival. Based on these results, it was expected that the debate over PORT in pN2 patients with NSCLC would come to an end. However, since pN2 patients have different clinicopathologic features, it has become more important to carefully select the patient population who will benefit from PORT. In addition, given the development of systemic treatments such as molecular-targeted therapy and immunotherapy, it is crucial to evaluate whether there is any benefit to PORT in the midst of these recent changes. Therefore, determining the optimal treatment approach for NSCLC pN2 patients remains a complex issue that requires further research and evaluation.

Keywords: Non-small cell lung cancer, pN2 stage, Postoperative radiotherapy, R0 resection

## Introduction

Cancer is the first leading cause of death in Korea and lung cancer accounts for 22% of cancer deaths with approximately 30,000 new cases diagnosed in 2019 [1]. In terms of histological type, 80%–90% of lung cancers are classified as non-small cell lung cancer (NSCLC) [2]. Stage I NSCLC has recently increased, but more advanced stages are still 70%, which need multimodal therapy [2].

Among NSCLC patients with positive nodes, especially pathological N2 (pN2) disease, 35%–55% experience treatment failures even after complete resection followed by adjuvant chemotherapy

and are associated with inferior overall survival (OS) [3,4]. According to the American Joint Committee on Cancer 8th edition, N2 is defined when metastasis is found in ipsilateral mediastinal and/or subcarinal lymph nodes [5]. With regard to the location and number of involved lymph nodes, N2 consists of a highly heterogeneous group. Besides, stage III pN2 possesses a wide variety of clinicopathologic features such as the size and characteristics of the primary tumor, making it more difficult to select patients who will benefit from postoperative treatments.

There has been a long debate regarding the appropriate use of postoperative radiotherapy (PORT) for patients with completely re-

sected NSCLC, although PORT is often employed for patients with pN2 NSCLC. Especially, the Lung ART trial presented in 2020 seemed to put an end to the controversy over PORT: no more PORT for stage IIIA pN2 after complete resection [6]. However, in 2021, the updated results of Lung ART reported that PORT significantly improved mediastinal relapse-free survival, despite no difference in metastasis-free survival [7]. Therefore, the authors concluded that a personalized prescription of PORT might be allowed based on prognostic factors.

In this review, we will not discuss PORT after incomplete resection (R1 or R2), which is a well-established PORT indication, and briefly summarize previous studies for PORT after R0 resection. We then highlight the major breakthroughs derived from recent randomized clinical trials (RCTs), updating current lung cancer treatment guidelines. Ultimately, we want to give answers about how to select and manage patients with completely resected pN2 NSCLC patients.

## Historical Perspective on PORT for N2 Stage NSCLC

Given the assumption that high local recurrence in pN2 patients than pN0-1 was thought to be due to the challenges of achieving complete surgical removal of microscopic lymph node metastasis in the mediastinum, a retrospective analysis was conducted at Mayo Clinic on a cohort of 224 patients with pN2 status between 1987 and 1993 to evaluate the potential benefit of PORT in these patients [8]. The 4-year freedom from local recurrence (83% vs. 40%, p < 0.0001) and survival rate (43% vs. 22%, p = 0.0005) were higher in the PORT group. This study published in 1997 was the largest evaluating PORT in pN2 patients in that era, suggesting that PORT can enhance both local control and OS. Large-scale RCTs have been initiated since that.

The landmark PORT meta-analysis in 1998, which initially included nine old RCTs (PORT vs. observation), showed unfavorable survival outcomes after PORT—OS, hazard ratio (HR) = 1.21, p = 0.001; disease-free survival (DFS), HR = 1.13, p = 0.007; locoregional relapse-free survival (LRRFS), HR = 1.16, p = 0.005 [9]. In subgroup analysis, PORT was detrimental with stages I–II, whereas, for stage III, there was no clear evidence of a detriment. After the publication of this meta-analysis, there was a sustained decline in PORT use. Consequently, few papers were published in early 2000. However, considering patients were recruited in the mid to late 1900s, this meta-analysis had several criticized points, despite the importance of this analysis. Participants might have been evaluated with inadequate staging and they received no longer standard treatment including old radiotherapy (RT) techniques such as co-

balt-60 equipment, large fraction size, and large treated volume with two-dimensional RT planning. In some trials included in the meta-analysis, the total dose was quite lower than the currently used, and adjuvant chemotherapy was not done.

Meanwhile, two studies published in 2006 made clinicians reconsider PORT for N2 NSCLC. The first one, the Surveillance, Epidemiology, and End Results (SEER) database analysis using 7,465 patients with resected NSCLC between 1998 and 2002 showed that although PORT was associated with a significant decrease in survival for patients with N0 and N1 disease, PORT was associated with more prolonged cancer-specific (5-year: 36% vs. 27%, p = 0.0298; HR = 0.850, p = 0.0133) and overall survival (5-year: 27% vs. 20%, p = 0.0036; HR = 0.855, p = 0.0077) for patients with N2 disease [10]. In addition, there was a post-hoc analysis of the Adjuvant Navelbine International Trialist Association (ANITA) trial, which was designed to compare the effect of adjuvant vinorelbine plus cisplatin with observation in completely resected NSCLC [11]. As PORT was not mandatory in this study, a non-randomized sub-analysis was conducted to compare OS in patients who did or did not receive PORT. The results showed that PORT led to longer OS, both in the chemotherapy arm (5-year: 47% vs. 34%) and in the observation arm in N2 disease (5-year: 21% vs. 17%).

Subsequent several retrospective studies have been published and they also suggested that a significant increase in DFS and 5%–15% of overall survival benefit was observed with PORT use in unselected N2 [12–14]. China multicenter retrospective study showed that the 5-year OS was 30.5% in the postoperative chemoradiotherapy group and 22.2% in the postoperative chemotherapy group (p = 0.007) [12]. For 5-year DFS, the postoperative chemoradiotherapy and postoperative chemotherapy group had a rate of 14.4% and 9.3%, respectively (p = 0.003). Another single institutional retrospective study showed that PORT had a significantly longer OS time (p = 0.046), DFS interval (p = 0.009), as well as significantly higher LRRFS (p = 0.025), distant metastasis-free survival rate (p = 0.001) [13]. Based on this, they conducted a PORT-C trial which will be discussed in a later section. The largest retrospective one was the US National Cancer Data Base (NCDB) study published in 2015. It included 4,483 patients with pN2 NSCLC who underwent complete resection and adjuvant chemotherapy from 2006 to 2010. On multivariable analysis, it demonstrated a similar gain of additional PORT (HR = 0.886) compared to the previous results of the SEER database: use of PORT was associated with an increase in median and 5-year OS compared with no PORT (median: 45.2 vs. 40.7 months, 5-year: 39.3% vs. 34.8%, p = 0.014) [14].

The steady advancement of RT delivery methods has raised expectations that modern PORT will contribute to improved survival. In the updated meta-analysis of 11 trials, a total of 2,387 patients

were included for survival analysis, and previous RCTs were stratified according to the use or non-use of linear accelerators (LINAC) [15]. In terms of local tumor failure, local recurrence significantly decreased with PORT, and the most significant decrease was observed in the group treated with LINAC only, with a relative risk (RR) of 0.31. With regard to OS, for the whole group, there was no improvement with PORT use. However, an increase in OS was observed in the LINAC-only group, with a RR of 0.76. PORT with LINACs was estimated to reduce local recurrence rates from 30% to 10% and PORT was estimated to increase the absolute 5-year OS by 13% (approximately 20% × 2/3 by generating a hypothesis model). These results reinforced further investigations of PORT using modern LINAC.

Lastly, the Cochran database review was published in 2016, updating the above-mentioned meta-analysis in 1998 with two trials conducted in Italy and Korea [16]. In this analysis, patients with T3N0M0 were reclassified from stage IIIA to stage IIB according to the TNM system change, and treatment bias was evaluated using the Fisher test. The results of 2,343 patients from 11 trials demonstrated that PORT showed a detrimental effect on patients with completely resected NSCLC. Besides, in contrast to the above meta-analysis, LINAC only did not affect OS (HR = 1.02, 95% confidence interval [CI] = 0.80-1.31, p = 0.85).

The aforementioned studies are summarized in Table 1.

## Recent Results of Representative RCTs on PORT for N2 Stage NSCLC

Several RCTs have been conducted on patients recruited in the recent 2000s, during which the advancement of imaging technology and treatment methods enabled more precise cancer staging, as well as, more sophisticated surgery and RT. In the following section, we will discuss four RCTs with a particular focus on the PORT-C and Lung ART trials, which were published in 2021 and 2022, respectively (Table 2).

The first RCT using modern PORT was conducted in China to compare adjuvant chemotherapy with adjuvant concurrent chemoradiotherapy (CCRT) in pN2 NSCLC [17]. Although this study has a

**Table 1.** Overview of historical studies investigating postoperative radiotherapy for non-small cell lung cancer

| Trial | Study design | Study period | n | Stage | Study arm | DFS | OS | Subgroup |
|---|---|---|---|---|---|---|---|---|
| Sawyer et al. [8] | Retrospective | 1987–1993 | 224 | pN2 | Observation vs. PORT (30–66.4 Gy) | 4-yr: 19% vs. 51% (p < 0.001) | 4-yr: 22% vs. 43% (p < 0.001) | OS: > 1 involved pN2, PORT favored |
| PORT Meta-analysis Trialists Group [9] | Meta-analysis | 1966–1995 | 2128 | I–III | Observation vs. PORT (30–60 Gy) | HR: 1 vs. 1.13 (p = 0.018) | HR: 1 vs. 1.21 (p = 0.001) | OS: Stage I, pN0, Observation favored |
| Lally et al. [10] | Retrospective | 1998–2002 | 7465 | II–III | Observation vs. PORT | – | 3-yr: 47% vs. 41% (p < 0.001) | DFS & OS: pN2, PORT favored |
| | | | | | | | | DFS 5-yr: 27% vs. 36% (p = 0.030) |
| | | | | | | | | OS 5-yr: 20% vs. 27% (p = 0.004) |
| Douillard et al. [11] | Post-hoc analysis | 1994–2000 | 840 | IB–IIIA | (Adjuvant chemotherapy was randomized) Observation vs. PORT (45–60 Gy) | – | POCT group (5-yr: 46% vs. 45%) Observation group (5-yr: 27% vs. 32%) | OS: pN2, PORT favored |
| | | | | | | | | POCT group (5-yr: 34% vs. 47%) |
| | | | | | | | | Observation group (5-yr: 17% vs. 21%) |
| Zou et al. [12] | Retrospective | 1998–2005 | 183 | III–pN2 | POCT vs. POCRT (48–54 Gy) | 5-yr: 9.3% vs. 14.4% (p = 0.003) | 5-yr: 22.2% vs. 30.5% (p = 0.007) | – |
| Dai et al. [13] | Retrospective | 2003–2005 | 221 | IIIA–pN2 | (Adjuvant chemotherapy not mandatory) Observation vs. PORT (60 Gy) | 5-yr: 16.5% vs. 32.1% (p = 0.009) | Median: 31.8 vs. 43.9 mo 5-yr: 30.6% vs. 36.6% (p = 0.046) | – |
| Robinson et al. [14] | Retrospective | 2006–2010 | 4483 | IIIA–pN2 | (After adjuvant chemotherapy) Observation vs. PORT (45–82.8 Gy) | – | Median: 40.7 vs. 45.2 mo 5-yr: 34.8% vs. 39.3% (p = 0.014) | – |

DFS, disease-free survival; OS, overall survival; pN2, pathological N2; PORT, postoperative radiotherapy; HR, hazard ratio; POCT, postoperative chemotherapy; POCRT, postoperative concurrent chemoradiotherapy.

**Table 2.** Summary characteristics of recent randomized clinical trials for postoperative radiotherapy in completely resected N2 stage non-small cell lung cancer

| Trial | Study period | n | Stage | Randomization | DFS | OS | Subgroup |
|---|---|---|---|---|---|---|---|
| Shen et al. [17] | 2004–2009 | 135 | IIIA-pN2 | POCT vs. POCRT (50.4 Gy/28 Fx) | Median: 18 vs. 28 mo | Median: 28 vs. 40 mo | OS: Multiple pN2, POCRT favored |
| | | | | | 5-yr: 18.8% vs. 30.3% (p = 0.04) | 5-yr: 27.5% vs. 37.9% (p = 0.07) | |
| Sun et al. [18] | 2009–2014 | 101 | IIIA-pN2 | POCT vs. POCRT (50 Gy/25 Fx) | Median: 21.9 vs. 24.7 mo (p = 0.40) | Median: 83.5 vs. 74.3 mo (p = 0.38) | OS: Never smoker, multiple pN2, POCT favored |
| PORT-C [19] | 2009–2017 | 364 | IIIA-pN2 | (After adjuvant chemotherapy) Observation vs. PORT (50 Gy/25 Fx) | mITT | mITT | DFS: Lymph nodes ≥ 4, PORT favored |
| | | | | | Median: 18.6 vs. 22.1 mo | Median: 81.5 mo vs. not reached | |
| | | | | | 3-yr: 32.7% vs. 40.5% (p = 0.20) | 3-yr: 82.8% vs. 78.3% (p = 0.93) | |
| | | | | | PP | PP | |
| | | | | | 3-yr: 30.6% vs. 42.8% (p = 0.05) | 3-yr: 83.1% vs. 82.6% (p = 0.41) | |
| Lung ART [20] | 2007–2018 | 501 | IIIA-pN2 | (Adjuvant chemotherapy not mandatory) Observation vs. PORT (54 Gy/27 Fx) | Median: 22.8 vs. 30.5 mo | 3-yr: 69% vs. 67% (NS) | DFS: Preoperative chemotherapy alone, PORT favored |
| | | | | | 3-yr: 44% vs. 47% (p = 0.18) | | |

DFS, disease-free survival; OS, overall survival; pN2, pathological N2; POCT, postoperative chemotherapy; POCRT, postoperative concurrent chemoradiotherapy; Fx, fraction; PORT, postoperative radiotherapy; mITT, modified intent-to-treat; PP, per-protocol; NS, not significant.

small number of patients due to slow accrual, three-dimensional conformal radiotherapy (3D-CRT) with optimal RT dose of 50.4 Gy in 28 fractions and modern chemotherapy regimen—paclitaxel (175 mg/m$^2$) and cisplatin (60 mg/m$^2$)—was applied. As a result, the adjuvant CCRT group showed decreased local (18/66 vs. 34/69, p = 0.01) and distant failures (32/66 vs. 45/69, p = 0.05) and improved DFS rate (5-year: 30.3% vs. 18.8%, p = 0.04) of these patients, compared with adjuvant chemotherapy. Despite the marginal significance of the difference, a superior OS was observed in the adjuvant CCRT group (5-year: 37.9% vs. 27.5%, p = 0.07), and in subgroup analysis, adjuvant CCRT increased the OS rate of patients with multiple N2 (p = 0.02).

A similar randomized phase II trial for only unsuspected or minimal N2 NSCLC was conducted in South Korea, reporting no significant differences in DFS and OS between adjuvant CCRT and chemotherapy alone [18]. The exploratory analysis of subgroups demonstrated that OS might be improved when patients with non-adenocarcinoma (HR = 0.359, 95% CI = 0.093–1.390) or with fewer than 15 lymph nodes dissected (HR = 0.575, 95% CI = 0.135–2.446) were treated with adjuvant CCRT. A cautious interpretation of this result needs because of a very small number of patients. Compared to the study by Shen et al. [17], the Korean study showed a higher OS, and the authors attributed this to the thorough staging workup and invasive mediastinal staging procedures. This difference in study populations might reduce the role of adjuvant RT in the Korean trial. Furthermore, there was a contrast

between the two groups that multistation pN2 patients favored chemotherapy alone in the Korean trial and CCRT in the Chinese study. Distant metastasis frequently occurred in multistation pN2 disease and the insufficient dose of chemotherapy in CCRT did not control distant metastasis properly, leading to decreased OS. Further validation is required. The number of patients experiencing locoregional failure only was 5 (9.8%) in CCRT and 7 (14.0%) in the chemotherapy alone.

The phase III PORT-C trial enrolled patients with completely resected N2 NSCLC and randomized 1:1 to PORT 50 Gy and observation after four cycles of adjuvant platinum-based chemotherapy [19]. Intensity-modulated radiotherapy (IMRT) was applied in 89% of patients. The primary endpoint was DFS. The clinical features were comparable between the two groups: 80% of patients had adenocarcinoma, and nearly 60% were not cN2 which underlies the importance of pretreatment mediastinal staging. The 3-year DFS rates in PORT and observation were 40.5% versus 32.7%, respectively, in the modified intent-to-treat analysis (HR = 0.84, 95% CI = 0.65–1.09, p = 0.20). In the per-protocol analysis, PORT significantly improved DFS (42.8% vs. 30.6%; HR = 0.75, 95% CI = 0.57–1.00, p = 0.05) but not OS (82.6% vs. 83.1%; HR = 0.83, 95% CI = 0.53–1.30, p = 0.41). The local recurrence-only was less observed in the PORT group compared to the non-PORT (3-year: 9.5% vs. 18.3%; Fine-Gray HR = 0.55, 95% CI = 0.31–0.97, Gray test p = 0.04). The authors described that no RT-related mortality was observed, and most deaths occurred due to cancer progression.

The low toxicity rate can be attributed to the use of IMRT and the implementation of stricter dose constraints for organs at risk. We need to take a closer look at which 44 of 184 patients (23.9%) in the PORT arm refused PORT, and 10 of 180 patients (5.6%) in the observation arm actually received PORT. Besides, although all patients completed four cycles of postoperative chemotherapy, 61.9% of patients still experienced distant metastasis. This may have offset the benefits of locoregional control from PORT, resulting in no improvement in DFS and OS.

Another phase III trial, the Lung ART trial, also randomized 1:1 to PORT of 54 Gy (3D-CRT of 89% and IMRT of 11%) and observation [20]. This trial did not meet the primary accrual goal due to slow enrollment. Baseline patient characteristics were comparable between the two groups. Major tumor histology was adenocarcinoma over 70%. Although over 90% of patients were staged with positron emission tomography-computed tomography scan, of enrolled cases, 40% had microscopic, unforeseen N2. And about 34% of the patients had single N2 station involvement. Adjuvant chemotherapy was not mandatory at that time and unlike the previous three studies, neoadjuvant chemotherapy was allowed. Nevertheless, the majority of patients (96%) were treated with chemotherapy (preoperative, postoperative, or both). In primary endpoint analysis, non-significant improvement of DFS was shown: 3-year DFS rate of 43.8% in control, higher than expected, and 47.1% with PORT; median DFS of 8 months increased by PORT (30.5 vs. 22.8 months; HR = 0.86, 95% CI = 0.68–1.08, p = 0.18). PORT did not increase OS. The control arm was much more likely to suffer mediastinal relapse (46.1% vs. 25%), which indicated approximately 50% risk reduction of locoregional failure by PORT, but intercurrent death was more common in the PORT arm (14.6% vs. 5.3%). Notably, 11 patients among 21 deaths in the PORT group died with cardiopulmonary toxicity and these may result from the most common application of 3D-CRT (89%). But the mean dose of heart was not different between patients with 3D-CRT and IMRT—median with interquartile range, 13.5 Gy (8–19) vs. 13.7 Gy (6–18), requiring more detailed analysis. Multivariable analysis identified the significant prognostic factors for DFS as follows: gender, histology, N1 involvement, number of involved mediastinal nodes, and quality of resection.

Overall, up-to-date PORT trials showed that it can reduce locoregional recurrence approximately by half after the standard treatment approach, but this locoregional control benefit may not be translated into DFS or OS benefit because of potential cardiopulmonary toxicity by 3D-CRT or unsatisfactory systemic control with platinum-doublet chemotherapy agents. Given that a subgroup analysis has demonstrated the benefits of PORT in certain patient populations, further research is necessary to define and characterize these patients.

## Current Guidelines and Recommendations on PORT for N2 Stage NSCLC

As discussed in the previous parts, robust evidence to support the use of PORT in the treatment of N2 stage NSCLC is still lacking. Currently, most international guidelines mention the use of PORT as follows: in the case of R1 or R2 resection, there is generally no big difference in the use of PORT, but for pN2 disease after R0 resection, the recommendation level is not high or it is suggested to apply selectively [21–24] (Table 3).

In the National Comprehensive Cancer Network guidelines, postoperative chemotherapy can be administered followed by PORT or concurrently depending on the margin status [21]. PORT is recommended with a category 2A for N2 after R0 resection. Although the American Society for Radiation Oncology (ASTRO) does not publish very up-to-date official guidelines after the publication of recent RCTs, in the previous guidelines they described that PORT addition after R0 resection in N2 disease showed no definitive proof of a positive or negative impact on OS but showed better local control than observation strategies [22].

**Table 3.** The latest recommendation in various guidelines for postoperative radiotherapy in completely resected N2 stage non-small cell lung cancer[a]

| Year | Guideline | Recommendation level[b] | Description |
|---|---|---|---|
| 2015 | ASTRO | Strong | May improve local control |
| 2017 | ESMO | C (optional) | May be an option following individual risk assessment |
| 2017 | ASCO | Moderate | Recommend a postoperative multimodality evaluation |
| 2022 | ASCO | Weak | Not routine use for patients without ECE who received platinum-based chemotherapy |
| 2023 | NCCN | Category 2A[c] | Consider RT |

ASTRO, American Society for Radiation Oncology; ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology; ECE, extracapsular extension; NCCN, National Comprehensive Cancer Network; RT, radiotherapy.
[a]At present, there are no official recommendations from the European Society for Radiotherapy and Oncology.
[b]This indicates the level of recommendation in the original guideline.
[c]Category 1: chemotherapy followed by atezolizumab or pembrolizumab or osimertinib.

However, the guidelines of the medical society including the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) more conservatively state that PORT use in R0 resection can be considered "only in selected cases" following individual risk assessment [23,24]. The ESMO recommends no routine use of PORT in single N2 status and only permits PORT after careful evaluation of locoregional recurrence risks [23]. In multistation N2, definitive CCRT is preferred but multidisciplinary approaches are required. According to the ASCO guidelines published in 2017, postoperative multimodal assessment is recommended to determine the advantages and disadvantages of receiving PORT [24]. Recently updated ASCO guideline mentions that PORT should not be routinely offered for patients receiving platinum-based chemotherapy either before or after surgery and without extracapsular extension (ECE) [25]. But, the strength of its recommendation is weak. ASTRO has released an updated article agreeing with this ASCO guideline [26].

Conclusively, in the current status, PORT is not recommended routinely for all patients with completely resected pN2 NSCLC. The decision on whether to use PORT should be made on an individualized basis, taking into account the risk factors presented in the following section.

## Factors Affecting the Choice of PORT for N2 Stage NSCLC: Implications for Patient Selection

There is still no robust answer in PORT patient selection, and various data exist for each study. Here are some of the most important factors to consider:

### 1. Multistation/extensive mediastinal involvement after mediastinal dissection

In the Lung ART trial, multiple mediastinal node stations were involved in about 30% of patients [20]. DFS was affected by ≥2 stations involved, compared with a single station (HR = 1.46, 95% CI = 1.1–1.9, p = 0.01). A previous study suggested a potential DFS benefit of PORT in patients with multiple station mediastinal lymph node metastases (5-year: 43.2% vs. 16.6%, p = 0.037) [27]. It also demonstrated in another retrospective study that PORT improved DFS in patients with multiple N2 stations metastases compared with single N2 station metastasis (5-year: 41.7% vs 5.9%, p = 0.0220) [28]. In regard to OS, patients with multiple pN2 favored postoperative CCRT over chemotherapy alone [17]. On the contrary, some investigators also claimed that single N2 station involvement was a predictor of benefit from PORT [29]. Although the number of patients was too small, the Korean trial reported that chemothera-

py alone (n = 8) was more effective than CCRT (n = 5) for patients with N2 multistation (OS: HR = 5.572, 95% CI = 1.01–30.754) [18].

### 2. The number of metastatic lymph nodes or lymph node ratio

In the SEER data analysis including 3,373 patients from 2004 to 2013, multivariable analysis showed that the number of positive lymph nodes (≤3) was independently associated with better OS and lung cancer-specific survival, then the use of PORT demonstrated better OS compared to no-PORT for patients with positive lymph nodes (>3), but not for patients with less number of positive lymph nodes (≤3) [30]. In terms of DFS, it also showed consistent results in the PORT-C (HR = 0.75, 95% CI = 0.58–0.98, p = 0.04) [19]. Other studies using the SEER data or NCDB showed that PORT can be indicated in patients with a specific range of lymph node-positive ratios [31–34]. The proposed cutoff for lymph node ratio varied among studies, with some suggesting a threshold of >15% [34], ≥30% [33], ≥50% [31], or 60%–80% [32].

### 3. ECE

Importantly, ECE has reflected the aggressive biological behavior in several types of cancers, including head and neck, breast, and colorectal cancers [35–37]. In patients with completely resected stage IIA–IIIA NSCLC, ECE also represents a powerful prognostic factor [38]. PORT led to a significant improvement in OS among negative ECE patients (HR = 0.518, 95% CI = 0.276–0.971, p = 0.04) but did not have a similar effect on positive ECE patients [39]. Although recently conducted RCTs did not evaluate the association between ECE and PORT [17–20], the status of ECE can potentially aid in selecting pN2 patients who will benefit from PORT. On the other hand, some argue that in cases where there is ECE or lymph node capsular rupture, the resection should be considered incomplete [40], and this may necessitate the use of PORT.

### 4. Histology (squamous cell carcinoma vs. adenocarcinoma)

There is a discrepancy regarding the NSCLC histology that shows the benefits of PORT. Several studies proposed that PORT may confer a greater advantage in treatment outcomes for squamous cell carcinoma [27,41]. They reported increases in the 5-year OS (from 37.1% to 63.2%, p = 0.026) and DFS (from 23.3% to 70.1%, p = 0.011) by PORT. But others found that the presence of the papillary predominant adenocarcinoma subtype was a reliable indicator of the potential benefit from PORT [29].

### 5. ypN2 in case of receiving neoadjuvant chemotherapy

Neoadjuvant chemotherapy is an alternative treatment option for

resectable NSCLC [21]. Patients with ypN2 status may have a greater extent of regional tumor involvement and increased chemotherapy resistance when compared to those with pN2 status. Thus, the use of PORT can potentially enhance locoregional management and ultimately improve overall survival [42]. Large-scale retrospective studies using SEER or NCDB suggested that PORT benefited patients with persistent N2 disease after neoadjuvant chemotherapy [34,42,43]. In the Lung ART trial, subgroup analysis revealed that PORT significantly improved DFS in ypN2 patients (3-year: 49.4% vs. 20.8%; HR = 0.52, 95% CI = 0.28–0.98) [20].

Several risk factors above can predict the benefit of PORT and can be considered when selecting patients. Several nomograms or scoring systems have been developed to help physicians screen and counsel patients with resected N2 [44–46]. As a simplified model of them, one article insisted that patients who meet three or more of the following criteria are strongly advised to undergo PORT: smoking index (number of cigarettes smoked per day × number of cigarette-years) ≤ 400, cN2, pT3, squamous cell carcinoma, and ≥ 4 positive nodes [44].

Although definite high-risk factors are still not consistently identified, PORT should not be completely disregarded in these patients as a potentially useful treatment option. Rather, it can be summarized that steady research efforts are needed in consideration of the future perspectives introduced in the next section.

## Ongoing Trials, Future Directions, and Conclusions

As summarized above, it is thought that more clinical evidence is still needed for the application of the PORT for pN2 patients, but the protracted length of adjuvant trials for the resectable stage of NSCLC has resulted in slow progress and high expenses. It is highly likely that the high-level evidence for PORT we currently had will not be updated for years. Japan Clinical Oncology Group 1916 (J-PORT study, UMIN000042905) is in progress using a scheme similar to the PORT-C trial, but we still have to wait several years to get another prospective randomized evidence [47].

From a different perspective, the clinical trial using stereotactic body radiotherapy (SBRT) in the adjuvant setting was launched in 2019 for patients with close/involved surgical margins or pN2 (NCT04073745). Considering SBRT has an extremely short treatment duration and fewer side effects compared with conventional RT, the positive results of this trial would broaden the PORT indications in NSCLC.

Another big change to consider is the development and change of systemic chemotherapy for resectable stage NSCLC. More recently, the promising progress in the treatment of metastatic NS-CLC has increased interest in using immune checkpoint blockades or targeted agents at resectable stages. IMpower010 made adjuvant atezolizumab maintenance one of the options after routine adjuvant chemotherapy [48]. Of course, the usual PORT that can be considered subsequently after adjuvant chemotherapy was not allowed under the IMpower010 research protocol. However, a considerable portion of enrolled patients subsequently required post-relapse mediastinal RT. These results suggest the possibility that there is still a role for PORT to further increase the therapeutic outcome.

In contrast, PORT may not be beneficial in patients with actionable mutations. The ADAURA trial found that the use of osimertinib after surgery significantly improved DFS in patients with epidermal growth factor receptor (EGFR) mutation-positive completely resected stage IB to III NSCLC (compared with placebo), therefore the additional benefit of PORT may be limited considering the high efficacy of osimertinib in EGFR mutation-positive stage III NSCLC [49].

Another important recent challenge to applying PORT is the increased use of the neoadjuvant approach led by the CheckMate 816 regimen [50]. Since many neoadjuvant trials did not include PORT in the protocol, there is very little evidence on how to apply PORT to patients who received these treatments. Hopefully, adopting perioperative immune checkpoint blockades can improve distant metastasis control and may re-consider the role of robust locoregional control by PORT.

Along with these, other ongoing trials of novel systemic therapy with targeted agents or immunotherapy may also change PORT indications. The contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment. If better systemic control were achieved and patterns of failure were changed, the role of PORT may be revisited. So far, in surgically resected NSCLC, the efficacy of systemic treatment varies from patient to patient due to various factors, and it is not possible to accurately determine whether PORT can improve survival under certain levels of systemic control. Further evidence is needed in the midst of these recent changes and adequately powered trials to establish clinically meaningful benefits are awaited.

In conclusion, PORT for completely resected pN2 NSCLC has been an area of ongoing debate. The first choice for pN2 NSCLC patients after complete resection had been PORT since the late 1990s; however, the Lung ART and PORT-C trials have challenged this notion. Despite demonstrating a noteworthy decrease in the locoregional recurrence rate, PORT has yet to produce any survival advantage. Nevertheless, the potential benefits of PORT for patients with high-risk features remain uncertain. Nevertheless, we cautiously recommend the use of PORT for N2 stage NSCLC patients with high-risk features, such as high and/or persistent mediastinal

tumor burdens. Future research should focus on identifying optimal candidates for PORT and determining its effectiveness in combination with novel systemic therapies. Ultimately, the goal is to establish clinically meaningful benefits for patients with completely resected pN2 NSCLC.

## Statement of Ethics

As this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Author Contributions

Conceptualization, Kim BH, Kim HJ. Supervision, Kim HJ. Writing of the original draft, Kim BH, Kim JS. Writing of the review and editing, Kim BH, Kim JS, Kim HJ.

## Data Availability Statement

Not applicable.

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