

# High Lymph Node Positive to Sampled Ratio as a Potential Indication for Postoperative Radiation Therapy in Patients with pN2 Non-small-cell Lung Cancer

Nikhil P. Mankuzhy<sup>1,2</sup>, Muayad F. Almahariq<sup>1</sup>, Craig W. Stevens<sup>1</sup>, Thomas J. Quinn<sup>1\*</sup>

<sup>1</sup>Department of Radiation Oncology, Beaumont Health, Royal Oak, MI, USA

<sup>2</sup>Oakland University William Beaumont School of Medicine, Rochester, MI, USA

\*Correspondence should be addressed to Thomas J. Quinn; Thomas.Quinn@beaumont.edu

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## Abstract

**Background:** The role for postoperative radiation therapy (PORT) for patients with non-small-cell lung cancer (NSCLC) with mediastinal lymph node (LN) involvement (pN2 disease) is controversial. We performed a SEER analysis comparing surgery alone with PORT among patients with pN2 NSCLC. As we await the final results of the LUNG ART trial, a subset of patients with a high LN positive to sampled (LPR) ratio may benefit from PORT.

**Patients/methods:** Patients with pN2 NSCLC, ranging from 1989-2016, were assessed from the Surveillance, Epidemiology and End Results (SEER) database. A propensity score (PS)-matched, inverse probability of treatment weighting (IPTW) analysis was conducted with multiple imputation with chained equations used for missing LN data.

**Results:** A total of 9,423 patients were included in this study (N=4,950 surgery alone; N=4,473 PORT). After adjusting for selection bias with IPTW; there was no improvement in overall survival (OS) (HR 0.99, P=0.76). However, a subset of patients with LPR ≥ 50% did have improved OS (HR, 0.90; P=0.01).

**Conclusion:** In a large retrospective SEER analysis, PORT is not associated with an OS improvement or detriment among patients with pN2 NSCLC. Indeed, preliminary results from the LUNG ART trial identified no difference in disease free survival (DFS) with hazard ratio (HR) of 0.85 (p=0.16) or in OS. We look forward to the final results of the LUNG ART trial to better delineate which subgroups of patients may benefit from PORT. Our study suggests that a high LPR may be a potential indication for PORT.

**Keywords:** Lung cancer; Postoperative radiation therapy; Adjuvant therapy; pN2 NSCLC; SEER

## Background

Despite advances in cancer treatment and screening, lung cancer remains the leading cause of cancer death in the United States [1]. The majority of cases are locally advanced non-small cell lung cancer (NSCLC), treatment of which usually includes a bi- or tri-modality therapy utilizing a combination of surgery, chemotherapy, and radiation therapy. For patients initially treated with surgery, use of postoperative radiation therapy (PORT) for completely resected NSCLC has remained controversial since the initial publication of the PORT meta-analysis in 1998 [2]. Stewart et al. reported an overall detriment of PORT on

overall survival (OS), which was proposed to be linked to factors outside of inferior cancer control, such as adverse treatment effects. However, no clear impairment to OS existed in patients found to have mediastinal lymph node involvement (pN2), leading to multiple single-institution and database registry analyses investigating this question. These studies are limited by indication bias inherent to retrospective design, but provided justification of continued use of PORT in pN2 disease. Despite absence of high-level evidence, PORT has remained standard of care for this subset of NSCLC due to benefits in locoregional control and OS as indicated by American Society for Radiation Oncology (ASTRO) practice guidelines [3].

Modern radiotherapy techniques such as 3D conformal RT (3DCRT) and intensity modulated RT (IMRT) have been developed to improve targeting of disease while sparing normal surrounding tissue. Prior analyses, including the PORT meta-analysis, utilized older techniques that have an increased risk of cardiopulmonary toxicity when treating the mediastinum. They also were limited by lack of systemic therapy data and narrow time ranges of inclusion. To this end, we conducted a contemporary analysis of the Surveillance, Epidemiology, and End Results (SEER) database to provide an updated perspective on the use of PORT for pN2 disease [4].

## Patients/Methods

Patients included in this analysis had a single primary, were diagnosed with NSCLC and underwent surgical resection with mediastinal lymph node involvement (pN2). As chemotherapy is proven to improve OS in patients regardless of receipt of PORT, its inclusion in our analysis offers a more comprehensive approach compared to prior SEER analyses [5]. Advanced statistical methodology with propensity score matching and inverse probability of treatment weighting was used to account

for indication bias and multiple imputations by chained equations replaced missing data regarding lymph node status to allow for thorough analysis.

## Discussion

Contrary to other retrospective studies, including two National Cancer Database (NCDB) analyses that utilized chemotherapy data and advanced statistical techniques [6,7], PORT did not improve survival in pN2 disease overall in our analysis (2-year OS 55.3% vs. 54.3%, P=0.99; 5-year OS 26.9% vs. 26.8%, P=0.82) (Table 1). Urban et al. performed a SEER analysis and found that PORT improved OS only for those patients with pN2 disease and lymph node ratio (LNR); however, they were not able to include receipt of chemotherapy in their analysis [8]. In our hands, the subset of patients with the proportion of sampled lymph nodes testing positive for disease of  $\geq 50\%$  were found to derive the most benefit from PORT (HR 0.90 [95% CI 0.84-0.97], P=0.01), regardless of receipt of systemic therapy (HR 0.91 [95% CI 0.82-1.00], P=0.09), as depicted in Table 1. Still these results suffer from limitations of use of national database registries. The retrospective nature could suffer from missing confounding variables,

Clinical Outcome	Result	P-Value
<b>All Patients (No PORT vs. PORT)<sup>1</sup></b>		
OS*	0.99 (0.95-1.00)	0.76
2-year survival <sup>^</sup>	55.3% vs. 54.3%	0.99
5-year survival <sup>^</sup>	26.9% vs. 26.8%	0.82
<b>Subgroup Analysis (No PORT vs. PORT)<sup>1</sup></b>		
LN-positive ratio $\geq 50\%$ *	0.90 (0.84-0.97)	0.01
Male patients*	0.94 (0.88-1.00)	0.04
Widowed patients*	1.16 (1.02-1.31)	0.02
<b>LN-positive ratio <math>\geq 50\%</math> (No PORT vs. PORT)<sup>1</sup></b>		
OS-All patients*	0.90 (0.84-0.97)	0.01
OS-Received chemotherapy*	0.91 (0.82-1.00)	0.09
<b>Multivariable Analysis<sup>2</sup></b>		
Positive LN ratio stratified (<50% vs. $\geq 50\%$ )*	1.46 (1.39-1.54)	<0.001
Chemotherapy (no/unknown vs. yes)*	0.88 (0.83-0.92)	<0.001
PORT (no vs. yes)*	0.98 (0.93-1.02)	0.30
<sup>1</sup> After PS matching with IPTW, <sup>2</sup> Doubly robust IPTW adjusted.* HR (95% CI), <sup>^</sup> Survival rate. Abbreviations: PORT, post-operative radiation therapy; OS, overall survival; LN, lymph node; PS, propensity score; IPTW, inverse probability of treatment weighting.		

**Table 1:** Summary of key findings from Mankuzhy et al. [4].

such as data on surgery margin status and sequence of chemotherapy, and it did not include details on intra- and extra-thoracic disease control.

Though PORT remained the standard of care for pN2 disease based on retrospective data, the LungART trial (NCT00410683) aimed to definitively answer this question in a randomized controlled trial with more modern RT techniques. Beginning in 2007, patients with confirmed pN2 disease at the time of surgery were enrolled to receive PORT with 3DCRT or no PORT after complete resection. The primary endpoint of the study was disease free survival (DFS). Results were recently presented at ESMO 2020 and published in abstract form [9]. They found that with a median follow up of 4.8 years, there was no difference in DFS with hazard ratio (HR) of 0.85 ( $p=0.16$ ), and median DFS of 30.5 months for PORT versus 22.8 months for no-PORT. The secondary endpoint of OS was also similar, with 3-year rates of 66.5% and 68.5% respectively. Although mediastinal relapse favored PORT (25% versus 46.1%), both early and late grade 3-5 cardiopulmonary toxicity was more common (7% and 20% versus 3.2% and 7.7%). These findings are generally consistent with our analysis, with no clear benefit of PORT shown for pN2 disease for all comers. The benefit of PORT for cancer control may be outweighed by the resultant toxicity and ensuing morbidity and mortality of high doses of radiation to critical organs in the thorax.

As we await the final publication of LungART, it is important to consider the spectrum that exists within pN2 disease. As illustrated by our analysis, patients with  $\geq 50\%$  sampled nodes positive did benefit from PORT with regards to OS, and likely represents the benefit of adjuvant RT for local control of a larger burden of mediastinal disease (Table 1). In this subset, risk of toxicity may be outweighed as preventing cancer related death is of higher priority. Use of post-operative chemotherapy likely contributes to the similar outcomes between the two arms of LungART and spares RT related toxicity to patients who do not derive benefit from aggressive local control. Though the conclusions of this trial indicate PORT should not be routine for all pN2 disease, identifying the subgroups that do benefit should be of interest. Further, as RT techniques continue to evolve, the capability to deliver increasingly conformal dose with more effective sparing of normal tissue may shift the therapeutic index. In LungART, patients received only 3DCRT as the modality of PORT, which does not spare organs at risk as well as IMRT or proton therapy. In patients receiving concurrent chemoradiation (CRT) for locally-advanced and unresectable NSCLC, IMRT is associated with decreased rates of  $\geq$  grade 3 pneumonitis and allows for lower dose to the heart [10]. Additional studies investigating IMRT and proton therapy are warranted, especially with the evolving systemic management of NSCLC [11]. The importance of adequate pre-treatment

mediastinal evaluation must be emphasized, as it can guide the decision for neoadjuvant therapy followed by surgery versus definitive CRT with adjuvant immunotherapy [12].

In the twenty years since the PORT meta-analysis was published, treatment of NSCLC after surgical resection remains a complex decision. While patients with positive margins after surgery may derive benefit, those with nodal disease require further study to adequately assess risk and benefit. Our paper shows that despite the lack of benefit overall, in certain populations, PORT could be indicated. Publication of the LungART can help guide these decisions and future studies as more data on subgroup analysis and dosimetry are reported. Going forward, a patient specific approach considering the new and evolving evidence is paramount to ensure optimal treatment of these patients.

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