Lymph Node Ratio May Predict the Benefit of Postoperative Radiotherapy in Non–Small-Cell Lung Cancer

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Introduction: The use of postoperative radiotherapy (PORT) after resection of non–small-cell lung cancer (NSCLC) is controversial, with some evidence suggesting a benefit in patients with N2 disease. We assessed lymph node ratio (LNR) as a predictor of PORT benefit.
Methods: By using the Surveillance, Epidemiology and End Results database, we analyzed resected, node-positive (N1–N2) NSCLC patients diagnosed between 1998 and 2009. LNR, (number of positive nodes/number of resected nodes) was categorized into four groups: LNR less than 12.5%, 12.5 to 24.9%, 25 to 49.9%, and 50% or more.
Results: Of 11,324 node-positive NSCLC patients identified, 6551 (57.9%) had N1 disease. The LNR was prognostic for survival in the entire cohort and within each nodal stage. The median survival in LNR groups 1, 2, 3, and 4 was 43, 40, 30, and 23 months in N1 disease and 40, 32, 27, and 22 months in N2 disease, respectively. PORT was associated with a worse survival on univariate analysis (hazard ratio [HR] =1.09; confidence interval [CI] 1.03–1.15; p = 0.002) but no effect on multivariate analysis (HR = 0.96; CI 0.90–1.02; p = 0.201). When analyzed by nodal stage, the benefit of PORT was limited to N2 disease (HR = 0.9; CI 0.84–0.99; p = 0.026) with no benefit in N1 disease (HR = 1.06; CI 0.97–1.15; p = 0.2). After stratifying by LNR, the survival benefit of PORT was limited to those with N2 disease and an LNR of 50% or more.
Conclusion: A high LNR is associated with a poorer survival in resected, node-positive NSCLC. The survival benefit associated with PORT in this disease seems to be limited to those with an LNR of 50% or more. This warrants further investigation in other cohorts and prospective studies.

Key Words: Non–small-cell lung cancer, Postoperative radiotherapy, Lymph node ratio.

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Lung cancer is the second most common cancer diagnosed and the most common cause of cancer death in both sexes in the United States.[1] Non–small-cell lung cancer (NSCLC) accounts for the majority of lung cancer cases. Treatment recommendations and prognosis are largely determined by the stage of cancer at diagnosis, with surgery typically recommended in early stage tumors.

After surgical resection, a finding of involved lymph nodes (LNs) is a significant prognostic factor and provides an indication for adjuvant chemotherapy.[2,3] The recommendation for adjuvant radiotherapy is more controversial. A previous meta-analysis suggested a detrimental effect of postoperative radiotherapy (PORT),[4] but the relevance of this study is uncertain in light of recent advances in radiation techniques, and other nonrandomized studies have suggested that patients with advanced nodal disease (ie., N2 disease) may benefit from PORT.[5,6] The American Joint Committee on Cancer Tumor Node Metastasis (TNM) lung cancer staging system classifies nodal stage based on the anatomical lymph node stations involved, irrespective of the absolute number of involved lymph nodes. Furthermore, it does not account for the number of LNs or LN stations examined, but recommendations that at least 6 to 10 lymph nodes or stations should be sampled have been suggested.[7,8]

The lymph node ratio (LNR), defined as the number of pathologically positive LNs divided by the number of LNs examined, has been proposed as a useful prognostic metric because it incorporates both the number of pathologically positive LNs and the number of LNs examined. The LNR has been shown to be prognostic in multiple malignancies, including breast cancer,[9] colon cancer,[10] and melanoma.[11] It has been shown to be prognostic in NSCLC,[12–15] but the majority of these studies have included patients diagnosed in the era before positron emission tomography (PET) or integrated PET/computer tomography (PET/CT). Furthermore, the LNR has been shown to be predictive of PORT benefit in oral cavity squamous cell carcinoma (SCC).[16]

The purpose of this study was to further validate the LNR in the modern PET and PET/CT era and to evaluate its ability to predict the survival benefit of PORT in resected NSCLC.

MATERIALS AND METHODS

The Surveillance, Epidemiology and End Results (SEER) program is a comprehensive source of population-based data

TABLE 1. Demographics of All Resected, Node-Positive NSCLC Diagnosed between 1998 and 2009

	All (N = 11,324)	LNR < 12.5% N = 2521 (22%)	LNR12.5–24.9,% N = 2869 (25%)	LNR 25–49.9% N = 3042 (27%)	LNR > = 50% N = 2892 (26%)	*p*
Age (yr)						0.25
<50	890 (7.9%)	180 (7.1%))	229 (8.0%)	238 (7.8%)	243 (8.4%)	
50–59	2556 (22.6%)	560 (22.2%)	642 (22.4%)	729 (24.0%)	625 (21.6%)	
60–69	3759 (33.2%)	863 (34.2%)	974 (34.0%)	948 (31.2%)	974 (33.7%)	
70–79	3370 (30%)	754 (29.9%)	827 (28.8%)	935 (30.7%)	854 (29.5%)	
80+	749 (6.6%)	164 (6.5%)	197 (6.9%)	192 (6.3%)	196 (6.8%)	
Sex						0.003
Women	5195 (45.9%)	1090 (43%)	1292 (45%)	1430 (47%)	1383 (48%)	
Year of diagnosis						<0.001
1998–2000	1997 (17.6%)	391 (15.5%)	428 (14.9%)	519 (17.1%)	659 (22.8%)	
2001–2003	2996 (26.5%)	592 (23.5%)	779 (27.2%)	799 (26.3%)	826 (28.6%)	
2004–2006	3127 (27.6%)	707 (28.0%)	797 (27.8%)	874 (28.7%)	749 (25.9%)	
2007–2009	3204 (28.3%)	831 (33%)	865 (30.2%)	850 (27.9%)	658 (22.8%)	
Race[a]						<0.001
White	9462 (83.7%)	2189 (86.9%)	2393 (83.5%)	2520 (83%)	2360 (81.6%)	
Black	1000 (8.8%)	178 (7.1%)	268 (9.4%)	290 (9.6%)	264 (9.1%)	
Other	850 (7.5%)	151 (6%)	205 (7.2%)	227 (7.5%)	267 (9.2%)	
Grade[b]						0.52
1	494 (4.7%)	103 (4.3%)	133 (4.9%)	137 (4.8%)	121 (4.5%)	
2	4244 (40%)	940 (39.6%)	1057 (39.2%)	1140 (40%)	1107 (41.1%)	
3	5452 (51.3%)	1221 (51.5%)	1385 (51.3%)	1473 (51.5%)	1373 (50.9%)	
4	434 (4.1%)	108 (4.6%)	123 (4.6%)	108 (3.8%)	95 (3.5%)	
Histology						<0.001
NSCLC, NOS	584 (5.2%)	134 (5.3%)	154 (5.4%)	161 (5.3%)	135 (4.7%)	
SCC	3460 (30.6%)	959 (38%)	985 (34.3%)	896 (29.5%)	620 (24.1%)	
Adenocarcinoma	4960 (43.8%)	934 (37.1%)	1177 (41%)	1357 (44.6%)	1492 (51.6%)	
BAC	574 (5.1%)	105 (4.2%)	134 (4.7%)	170 (5.6%)	165 (5.7%)	
Adeno with mixed subtypes	1175 (10.4%)	240 (9.5%)	267 (9.3%)	316 (10.4%)	352 (12.2%)	
Large-cell	571 (5%)	149 (5.9%)	152 (5%)	142 (4.7%)	128 (4.4%)	
Laterality[c]						0.13
Right	6102 (53.9%)	1348 (53.5%)	1532 (53.4%)	1609 (53%)	1613 (55.8%)	
Surgery[d]						<0.001
Lobectomy	9168 (81.1%)	1928 (76.6%)	2306 (80.4%)	2488 (81.9%)	2446 (84.8%)	
Pneumonectomy	2140 (18.9%)	590 (23.4%)	561 (19.6%)	551 (18.1%)	438 (15.2%)	
T stage[e]						0.001
1	2759 (26.1%)	591 (24.9%)	707 (26.2%)	744 (26.2%)	717 (26.9%)	
2	5757 (54.4%)	1328 (56%)	1490 (55.1%)	1552 (54.7%)	1387 (52.1%)	
3	796 (7.5%)	190 (8%)	220 (8.1%)	209 (7.4%)	177 (6.7%)	
4	1263 (11.9%)	263 (11.1%)	285 (10.6%)	335 (11.8%)	380 (14.3%)	
N-stage						<0.001
1	6551 (57.9%)	1800 (71.4%)	1793 (62.5%)	1660 (54.6%)	1298 (44.9%)	
2	4773 (42.2%)	721 (28.6%)	1076 (37.5%)	1382 (45.4%)	1594 (55.1%)	
RT[f]						<0.001
No PORT	7256 (70.7%)	1858 (81.3%)	1934 (74.2%)	1861 (67.4%)	1603 (61.3%)	
PORT	3011 (29.3%)	428 (18.7%)	672 (25.8%)	900 (32.6%)	1011 (38.7%)	
LN examined						<0.001
<10	5876 (51.9%)	240 (2.1%)	1527 (13.5%)	1865 (16.5%)	2244 (19.8%)	
> = 10	5448 (48.1%)	2281 (20.1%)	1342 (11.9%)	1177 (10.4%)	648 (5.7%)	

[a]Data on race were missing for 12 patients
[b]Grade was available for 10,624 patients.
[c]Laterality was available for 11,315 patients.
[d]Data about type of surgery were available for 11,308 patients.
[e]T-stage was available for 10,575 patients.
[f]RT data were available for 10,267 patients.
LN, lymph node; LNR, lymph node ratio; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified; BAC, bronchoalveolar carcinoma; RT, radiotherapy; PORT, postoperative radiotherapy; SCC, squamous cell carcinoma.

