Scientific Article

Predictors of relapse and evaluation of the role of postoperative radiation therapy in a modern series of patients with surgically resected stage III (N2) non—small cell lung cancer

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Abstract

Purpose: For patients with stage III (N2) non—small cell lung cancer (NSCLC) treated with surgical resection, postoperative chemotherapy improves overall survival (OS), but the role of postoperative radiation therapy (PORT) is controversial. The purpose of this study was to evaluate risk factors for local-regional recurrence and to evaluate the impact of PORT on local-regional control (LRC) and OS in a modern series of patients with surgically resected stage III (N2) NSCLC.

Methods and materials: A retrospective review was performed of patients with Stage III (N2) NSCLC who underwent curative intent resection at our institution between February 1999 and January 2012. OS, LRC, and metastasis-free survival were estimated from the date of surgery using the Kaplan Meier method.

Results: A total of 71 patients were included in the study. Patient median age was 63 years. Histology was adenocarcinoma in 69% of patients. Pretreatment positron emission tomography/computed tomography staging was performed for 90% of patients, and preoperative chemotherapy was administered in 23%. The rate of R0 resection was 96%. Forty-one patients (58%) received PORT and the median PORT dose was 50 Gy (range, 41.4-60 Gy). The median follow-up time for living patients was 5.0 years. Five-year OS for all patients was 66%. OS at 5 years for patients who received PORT compared with patients who did not receive PORT was 71% versus 60%, respectively (hazard ratio [HR], 0.61; 95% CI, 0.30-1.44; $P = .28$). LRC at 5 years for patients who received PORT compared with patients who did not receive PORT was 89% versus 76%,

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respectively (HR, 0.44; 95% CI, 0.13-1.45; $P = .17$). Factors associated with decreased LRC were male sex ($P = .011$) and primary tumor (pT) stage (pT3/4 vs. pT1/2, $P = .006$). Metastasis-free survival at 5 years for patients who received PORT compared with those who did not receive PORT was 62% versus 63%, respectively (HR, 1.07; 95% CI, 0.51-2.40; $P = .86$).

Conclusions: In this modern series of patients with resected stage III (N2) NSCLC, patients who received PORT had higher rates of OS and LRC, but these differences were not statistically significant.

Introduction

For patients with non−small cell lung cancer (NSCLC) who undergo curative-intent surgical resection, the presence of lymph node involvement increases the risk of local-regional recurrence (LRR) and distant metastases (DM).[1] Postoperative therapies, including postoperative chemotherapy (POCT) and postoperative radiation therapy (PORT), have been used in an attempt to reduce the risk of recurrence. Several randomized clinical trials, including a meta-analysis of 5 trials, have demonstrated a significant improvement in overall survival (OS) with the use of cisplatin-based POCT for lymph node positive NSCLC, with an absolute benefit in OS of 5% at 5 years.[2] However, the role of PORT for NSCLC remains controversial. A meta-analysis published in 1998 including 9 older clinical trials suggested that PORT has a significant adverse effect on the survival of patients with pN0 and pN1 NSCLC and no benefit or detriment for patients with pN2 disease.[3] Several well-recognized limitations of this meta-analysis limit its applicability to current practice, including the use of older radiation therapy (RT) techniques, limited use of chemotherapy, cohorts of patients with a predominately squamous cell histology, and use of older surgical and staging techniques. Specifically, older RT techniques may have had an unfavorable therapeutic ratio related to excessive RT delivered to normal tissues (heart and/or lungs) and inadequate RT delivery to residual subclinical local-regional disease.

More contemporary data suggest a potential benefit of PORT in patients with pN2 disease. A meta-analysis restricted to trials that used linear accelerator−based treatment and conventional dose and fractionation showed improvements in local control and OS for patients treated with PORT.[4] A secondary analysis of the Adjuvant Navelbine International Trialist Association trial also demonstrated improved OS for patients with pN2 disease who received PORT with or without POCT.[5,6] A Surveillance Epidemiology and End Result Program analysis of 7465 patients with NSCLC showed improved OS for patients with pN2 disease who received PORT but inferior OS for patients with pN0 or pN1 disease who received PORT.[7] Additionally, in an analysis of 4483 patients in the National Cancer Database with pN2 NSCLC who underwent curative-intent surgical resection and POCT between 2006 and 2010, PORT was associated with a significant improvement in OS.[8] Most recently, Shen et al[9] reported the outcomes of a prospective, randomized study that evaluated the role of PORT for treatment of stage IIIA NSCLC. Although the trial closed early due to slow accrual, patients who received PORT had a statistically significant improvement in local and distant control but not in OS.

Despite inconsistent evidence, current National Comprehensive Cancer Network (NCCN) guidelines recommend sequential POCT and PORT after R0 resection of pN2 NSCLC.[10] Given the controversy regarding the role of PORT for treatment of pN2 NSCLC and the questionable applicability of older studies to current practice, we examined our recent institutional experience with PORT in this patient cohort. We hypothesized that in this modern cohort, treatment with PORT (vs. no PORT) would be associated with improved local control and survival.

Methods and materials

Our institutional review board approved this retrospective study.

Patient selection

We reviewed the medical records of all patients who underwent a curative-intent resection for stage IIIA or IIIB NSCLC at our institution between February 1999 and January 2012. Patients with pathologically confirmed N2 disease were included. This included patients with biopsy-proven cN2 disease (as determined by mediastinoscopy, Chamberlin procedure, and/or endoscopic ultrasound-guided biopsies) who received neoadjuvant chemotherapy. Patients with pN2 disease who did not receive neoadjuvant therapy were also included in the study. Exclusion criteria were histology other than NSCLC, other concurrent malignancy, receipt of neoadjuvant RT, R2 resection, no PORT or POCT, or inadequate follow-up or documentation.

Patient evaluation and treatment

Clinical staging typically consisted of a computed tomography (CT) scan of the chest, abdomen, and pelvis; a magnetic resonance imaging scan of the brain; and whole body positron emission tomography (PET)/CT scan (starting in 2002). Preoperative mediastinal staging with mediastinoscopy, Chamberlin procedure, and/or endoscopic ultrasound-guided biopsy was performed on a case-by-case basis. Neoadjuvant chemotherapy was considered for select patients with biopsy-proven clinical N2 disease. Surgical resection typically consisted of a lobectomy (if feasible) and a hilar and mediastinal lymphadenectomy. All patients in this series underwent an R0 or R1 resection. Staging was assigned in accordance with the American Joint Committee on Cancer, 7th edition.

Use of POCT and/or PORT was at the discretion of the treating oncologists. POCT typically consisted of a platinum-based doublet. For patients who received both POCT and PORT, treatments were typically administered in a sequential manner (ie, POCT followed by PORT). For patients who received PORT at our institution, CT-based planning was used. The RT target volume most frequently included the bronchial stump, ipsilateral hilar lymph node stations, and involved and at-risk (anatomically adjacent) mediastinal lymph node stations, which is similar to the guidelines used for the Lung Adjuvant Radiotherapy Trial (NCT00410683).[11] The staple or suture line was typically only included if there were positive surgical margins. Three-dimensional conformal or intensity modulated RT techniques were used. Typical dose volume constraints included a spinal cord maximum of <45 Gy, heart V35% <50%, and lung mean <20 Gy and V20 <35%.[12,13]

Outcomes assessment

Acute (ie, within 90 days of completion of PORT) and chronic (ie, more than 90 days after the completion of PORT) adverse events related to PORT that were documented in the medical records were scored using National Cancer Institute Common Toxicity Criteria Assessment of Adverse Events, Version 4.03. LRR was defined as clinical and/or biopsy-proven recurrence within the radiation field for patients treated with PORT or within the bronchial stump, ipsilateral hilum, or mediastinum for patients treated with POCT. All other sites of recurrence were considered DM. LRR included recurrence that was diagnosed prior to, concurrent with, or after diagnosis of DM. Local-regional control (LRC) was defined as the absence of LRR.

Statistical analyses

Fisher's exact or χ^2 tests were used to assess the association between patient/disease characteristics and receipt of PORT. The χ^2 tests were used for all variables except when a two-by-two comparison was performed, in which case a Fischer's exact test was used. OS, LRC, and metastasis-free survival (MFS) were estimated from the date of surgery using the Kaplan Meier method. Univariate analyses were performed to assess the association between patient/treatment variables (Table 1) and outcomes using Cox proportional hazards regression models. Multivariate analyses were not performed because of the sample size. Statistical significance was defined as $P <$ .05 using two-tailed tests. Statistical analyses were performed with JMP software (SAS Institute Inc, Cary, NC).

Results

Patient and treatment characteristics

A total of 71 patients were included in this study. The median follow-up time for living patients was 5.0 years (range, 0.6-15.4 years). Patient and treatment characteristics are detailed in Table 1. A total of 64 (90%) patients were clinically staged with PET/CT imaging scans. Neoadjuvant chemotherapy was administered to 16 patients (23%), of whom 75% received carboplatin and paclitaxel, mostly commonly for 3 cycles. The primary tumor resections were lobectomy (83%), pneumonectomy (11%), or wedge resection (6%). Two patients with biopsy-proven cN2 had negative pN2 nodes after induction chemotherapy. The most frequent POCT regimen was carboplatin and paclitaxel, with most patients receiving 4 cycles (range, 1-6). Neoadjuvant chemotherapy only, POCT only, or both neoadjuvant and POCT were administered to 13%, 58%, and 10% of patients, respectively. In total, 81% of patients received chemotherapy in the preoperative and/or postoperative setting. Forty-one patients (58%) received PORT, which was administered at our institution in 71% of cases. The median PORT dose was 50 Gy (range, 41.4-60 Gy) and the median dose per fraction was 2 Gy (range, 1.8-2.1 Gy). The most common dose/fractionation regimens were 50 Gy/25 fractions (51%) and 50.4 Gy/28 fractions (27%). The RT technique was 3-dimensional conformal (88%) or intensity modulated radiation therapy (12%). Two patients received chemotherapy concurrent with PORT, and one of these patients had an R1 resection.

Factors associated with the use of PORT

No receipt of chemotherapy ($P = .0002$) and younger age ($P = .0029$) were significantly associated with increased likelihood of receiving PORT (Table 1).

Outcomes

For all patients, OS at 5 years was 66%. OS at 5 years for patients who received PORT compared with patients

Table 1 Patient and treatment characteristics

| Characteristics	All Patients N = 71	PORT n = 41	No PORT n = 30	P-Value
Sex				.15
Male	56%	49%	67%	
Female	44%	51%	33%	
Age, median (range), years	63 (36-80)	60	66.5	.003
ECOG performance status				.77
0	89%	88%	90%	
1	11%	12%	10%	
Histology				.95
Adenocarcinoma	69%	68%	70%	
Squamous cell carcinoma	28%	29%	27%	
Clinical tumor stage				.08
T1-2	79%	71%	90%	
T3-4	21%	29%	10%	
Clinical node stage				.18
N0	52%	51%	53%	
N1	4%	7%	0%	
N2	44%	41%	47%	
Preoperative chemotherapy				.15
Yes	23%	29%	13%	
No	77%	71%	87%	
Surgical procedure				.56
Pneumonectomy	13%	15%	10%	
Other	87%	85%	90%	
Number of pN2 nodes, median (range)	2 (1-15)	2 (0-12)	1.5 (0-15)	.71
Number of involved N2 stations, median (range)	1 (0-3)	1 (0-3)	1 (0-2)	.67
Extranodal extension				.69
Yes	8%	7%	10%	
No	92%	93%	90%	
Surgical margins				.26
Positive	4%	7%	0%	
Negative	96%	93%	100%	
Underwent chemotherapy (pre- or postoperative)				.0002
Yes	80%	66%	100%	
No	20%	34%	0%	

ECOG, Eastern Cooperative Oncology Group; PORT, postoperative radiation therapy.

who did not receive PORT was 71% versus 60%, respectively (hazard ratio [HR], 0.61; 95% CI, 0.30-1.44; $P = .28$; Fig. 1). Univariate analysis revealed that an increased number of positive lymph nodes was the only factor significantly associated with risk of death (HR, 1.10; 95% CI, 1.01-1.17; $P = .028$). For all patients, LRC at 5 years was 84%. LRC at 5 years for patients who received PORT compared with patients who did not receive PORT was 89% versus 76%, respectively (HR, 0.44; 95% CI, 0.13-1.45; $P = .17$; Fig. 2). Univariate analysis revealed that factors that were significantly associated with decreased LRC were male sex (HR, 9.3; 95% CI, 1.77-170.1; $P = .005$) and pT3/4 compared with pT1/2 (HR, 5.73; 95% CI, 1.69-20.37; $P = .006$). For all patients, MFS at 5 years was 62%. MFS at 5 years for patients who received PORT compared with patients who did not receive PORT was 62% versus 63%, respectively (HR, 1.07; 95% CI, 0.51-2.40; $P = .86$; Fig. 3).

We performed further analyses in the subset of patients who received only POCT (n = 41) with or without PORT, excluding patients who received neoadjuvant chemotherapy or did not receive any chemotherapy. OS at 5 years for patients who received PORT (n = 15) compared with patients who did not receive PORT (n = 26) was 80% versus 62%, respectively (HR, 0.47; $P = .20$). LRC at 5 years for patients who received PORT compared with patients who did not receive PORT was 79% versus 81%, respectively (HR, 1.17; $P = .82$).

Adverse events associated with PORT

A majority of patients (80%) experienced one or more acute adverse events during treatment with PORT, but only one patient (2%) had a grade 3 or higher acute adverse event (grade 3 esophagitis). Grade 2 acute adverse events occurred in 51% of patients and included
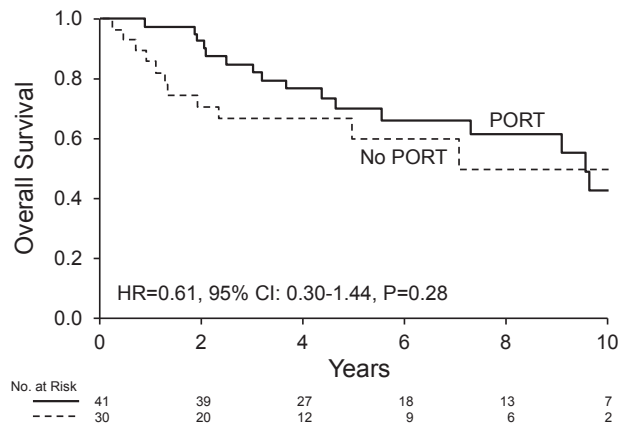
Figure 1 Overall survival for patients receiving post-operative radiotherapy (PORT) versus no PORT.
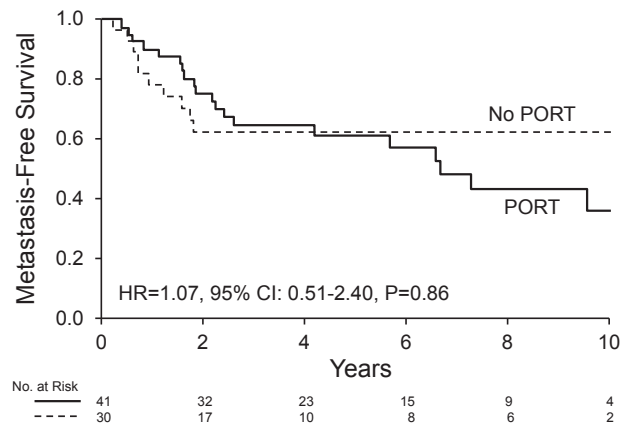
Figure 3 Metastasis-free survival for patients receiving post-operative radiotherapy (PORT) versus no PORT.

esophagitis (44%) and dermatitis (17%). Late adverse events were recorded in 46% of patients, but no patients had a grade 3 or higher late adverse event. Grade 2 late adverse events occurred in 24% of patients and included pneumonitis (15%), esophagitis (7%), and fibrosis (5%). Two patients experienced radiation pneumonitis that required treatment with oral steroids.

Discussion

Several observations can be made from this contemporary series of patients with surgically resected stage III (N2) NSCLC who received adjuvant therapy. The 5-year OS was 66%, which compares favorably to historical data from our institution and others.[3,4,7,14] Patients who received PORT had higher LRC and OS when compared with patients who did not receive PORT, although these differences were not statistically significant. Given the sample size, we cannot exclude the possibility of a potentially meaningful benefit (or detriment) for PORT in

this context. Factors associated with poorer LRC were male sex and higher tumor stage. Modern PORT was well tolerated with a low frequency (2%) of grade 3 adverse events and no grade 4 or higher adverse events.

This study has several strengths relative to other published analyses. This was a modern cohort that reflects contemporary surgical, chemotherapy, and RT techniques and regimens at a high-volume tertiary care cancer center. Furthermore, PET/CT scan staging was done for the vast majority of patients (90%), which is reflective of current practice and in accordance with NCCN guidelines. These attributes support the applicability of these findings to current practice. We did not identify any significant differences in patient and treatment characteristics in the PORT and no-PORT treatment cohorts among the factors examined except for younger age and no receipt of chemotherapy in the PORT cohort, which suggests that the cohorts were reasonably well balanced.

Several weaknesses of this study should be recognized. First, because the study is retrospective in nature, there are potential biases related to the decision to treat with POCT and/or PORT. Second, the cohort is modest in size, which limits our ability to detect potential statistically and clinically significant differences between the PORT and no-PORT treatment groups. Additionally, the limited sample size prevents us from performing multivariate and propensity-matched analyses to try to limit potential biases in this retrospective analysis. The small sample size likely is a result of improved preoperative staging techniques for detection of cN2 disease, including endoscopic ultrasound (bronchial and/or esophageal) and PET/CT scans, because patients with cN2 disease are preferentially treated at our institution with neoadjuvant or definitive chemoradiation therapy instead of initial surgery. Over a similar timespan at our institution, 80 and 112 patients with stage IIIA (N2) NSCLC were treated with curative-intent trimodality therapy and curative-intent definitive chemoradiation therapy, respectively, compared with 71 patients in the present study treated with surgery and postoperative
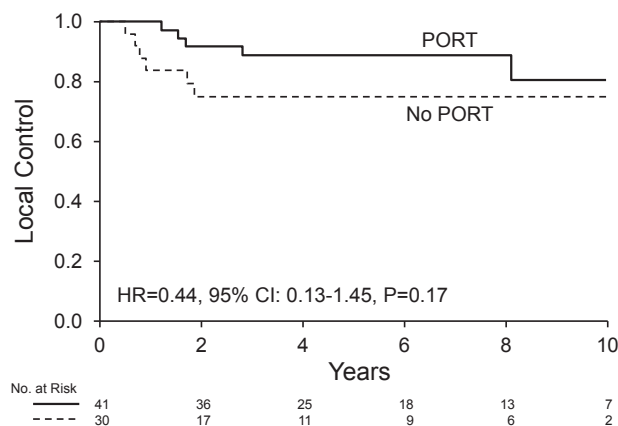
Figure 2 Local control for patients receiving post-operative radiotherapy (PORT) versus no PORT.

Table 2   Selected contemporary studies reporting outcomes after PORT for resected stage IIIA (pN2) non—small cell lung cancer

Author (year)	PORT	No. of Patients	Chemotherapy (%)	Overall Survival		Local-regional recurrence	
				3 years (%)	*P*-value	(%)	*P*-value
Douillard et al[6]	No	70	100	~41	–	26	–
	Yes	48	100	~59		15	
Shen et al[9]	No	69	100	~38	.07	49	.009
	Yes	66	100	~59		27	
Robinson et al[8]	No	2633	100	55	.014	–	–
	Yes	1850	100	59		–	
Current study	No	30	100	67	.86	24	.17
	Yes	41	66	83		11	

PORT, postoperative radiation therapy.

adjuvant therapy.[15] This likely explains the favorable survival rates that are observed in this selected, favorable-risk cohort of patients with stage III (N2) NSCLC. Additionally, 37% of patients in the PORT group did not receive chemotherapy (either adjuvant or neoadjuvant) due to contraindications or patient refusal, which may have adversely affected LRR and OS outcomes in the PORT group. In light of these limitations, these results should be considered to be hypothesis-generating and not definitive.

The Lung Adjuvant Radiotherapy Trial (NCT00410683) is an ongoing, randomized phase 3 clinical trial for patients with completely resected stage III (pN2) NSCLC in which patients are randomized to PORT or no-PORT treatment groups. Modern RT techniques are used, including CT-based treatment planning, standardized target delineation, linear accelerated-based treatment delivery, and conventional dose/fractionation (54 Gy in 27 fractions). The primary endpoint for this trial is disease-free survival and secondary endpoints include local control, OS, patterns of relapse, second cancers, and treatment-related toxicity.[16] The results from this trial will hopefully provide much-needed high-quality data on the role of PORT in the treatment of patients with NSCLC.

As we await more definitive data, results from our study and others support discussing treatment with PORT with patients who have surgically resected stage III (N2) NSCLC (Table 2). At our institution, POCT and PORT currently are routinely recommended for patients with R1/R2 resection, consistent with NCCN guidelines and recent observational data.[10,17] For patients with an R0 resection, initial POCT is recommended, followed by restaging and multidisciplinary discussion regarding the role of PORT. PORT is considered on a case-by-case basis and may be recommended particularly for patients with good performance status, close margins, advanced T stage, limited lymph node dissection, and/or multiple station N2 disease. However, further studies are needed to better define patient subsets that are more likely to derive benefit from PORT.[17,18] Additionally, molecular markers are needed to identify patients who are at a higher risk for LRR versus

DM recurrence. With more effective systemic therapies that are capable of controlling DM, control of local-regional disease may become increasingly important.

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