Mediastinal radiotherapy after adjuvant chemotherapy for resected non–small cell lung cancer with N2 lymphadenopathy: A novel meta-analysis

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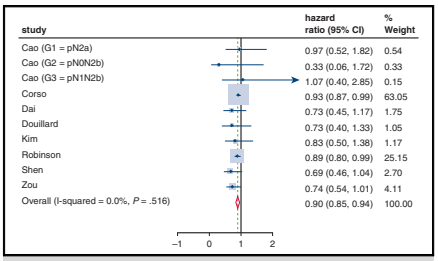
ABSTRACT

Introduction: Treatment for stage IIIA N2 non–small cell lung cancer (NSCLC) typically involves a combination of chemotherapy, radiotherapy, and surgery, but the optimal sequencing is not determined. Local recurrence rates following surgery remain high, and the role of postoperative radiotherapy (PORT) in N2 disease is unclear. This meta-analysis aims to determine whether PORT provides additional survival advantage beyond observation for patients with stage IIIA N2 disease who have undergone complete surgical resection and received adjuvant chemotherapy.

Methods: All studies comparing adjuvant chemotherapy and PORT versus adjuvant chemotherapy alone after curative surgical resection for stage IIIA N2 NSCLC were included. Meta-analysis was performed using random effects modelling in accordance with MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) guidelines. Subgroup analysis, heterogeneity, and risk of bias were assessed, with meta-regression to determine the effects of patient and tumor characteristics on outcomes.

Results: Ten studies with a pooled dataset of 18,077 patients (5453 PORT, 12,624 no PORT) were included. PORT significantly improved both overall survival (OS) and disease-free survival (DFS) at 1 year (OS: hazard ratio [HR], 0.768; DFS: HR, 0.733), 3 years (OS: HR, 0.914; DFS: HR, 0.732), and 5 years (OS: HR, 0.898; DFS: HR, 0.735, all $P < .0001$). These effects were independent of specific patient or tumor characteristics.

Conclusions: This study demonstrates a significant DFS and OS benefit from the addition of PORT following adjuvant chemotherapy. We advocate the consideration of PORT for such patients following specialist multidisciplinary assessment and comprehensive discussion of the benefits and risks of treatment. (JTCVS Open 2021;5:121-30)



PORT significantly improves survival at 5 years in patients with stage IIIaN2 NSCLC.

CENTRAL MESSAGE

The addition of postoperative radiotherapy as part of trimodality treatment following surgical resection and adjuvant chemotherapy improves survival outcomes in patients with stage IIIaN2 NSCLC.

PERSPECTIVE

The sequence and timing of multimodality therapy in stage III NSCLC is debated, with high post-resection local recurrence rates despite adjuvant chemotherapy. The role of PORT is controversial; however, it may confer a survival advantage in patients with stage IIIAN2 disease. This study addresses the question of PORT specific to stage IIIAN2 patients, demonstrating improved survival outcomes.

See Commentaries on pages 131 and 133.

Survival from non–small cell lung cancer (NSCLC) has improved in recent decades owing to advances in detection, surgical technique, radiotherapy, and systemic therapies,[1] but these improvements have been modest, and NSCLC remains the leading cause of cancer death in the Europe and the United States.[2] Treatment options include surgical resection, radiotherapy, cytotoxic chemotherapy, and immunotherapy, which are offered alone or in combination according to the stage of disease, intent of treatment, and patient fitness.

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Abbreviations and Acronyms

CI = confidence interval
DFS = disease-free survival
HR = hazard ratio
NSCLC = non–small cell lung cancer
OS = overall survival
PORT = postoperative radiotherapy
RR = risk ratio

Stage III disease[3] comprises a heterogeneous group of presentations often requiring 2 or more modalities of treatment given in combination or sequentially with debate on the appropriate sequencing and timing of treatments.[4,5] Patients with N2 disease (involvement of lymph nodes including but not beyond ipsilateral mediastinal and/or subcarinal stations) are of particular interest, with poor 5-year survival.[2,6,7] It is known that the affected station, number of stations, and presence of bulky disease all impact prognosis[8] and current guidelines therefore mandate full mediastinal staging with positron emission tomography–computed tomography and appropriate nodal sampling by endobronchial ultrasound-guided fine-needle aspiration or mediastinoscopy[8,9] ahead of radical treatment.

Trimodality treatment for operable N2 disease is becoming more standard practice for operable disease,[10,11] particularly as advances in surgical technology permit improved resection rates.[12] Although patients may receive chemoradiation as definitive treatment,[13] many with stage IIIA N2 disease receive surgery as a first definitive treatment either as a planned intervention or because occult N2 disease is found within the histologic specimen. Local recurrence rates following surgery remain high despite the proven benefits of adjuvant chemotherapy.[14-17] The role of postoperative radiotherapy (PORT) is more open to debate[18]: PORT was detrimental to survival in N0/1 disease but showed a nonsignificant survival advantage in N2 disease,[19] thus PORT is commonly but not uniformly used for patients with resected N2 disease. This analysis is over 20 years old and dates from a time when most patients received no adjuvant chemotherapy and when radiotherapy techniques were more rudimentary than current practice.

This meta-analysis was conceived to determine whether modern PORT provides an additional survival advantage beyond observation for patients with completely resected stage IIIA N2 disease who have received adjuvant chemotherapy.

METHODS

Literature Search

A literature search was performed using PubMed, Ovid, Embase, clinicaltrials.gov, Google Scholar, and Cochrane databases to identify all published and unpublished trials in any language. No date restrictions were placed on articles. The "related articles" function was used to broaden the search, and all abstracts, studies, and citations scanned and reviewed.

Inclusion and Exclusion Criteria

All studies directly comparing adjuvant chemotherapy and PORT versus adjuvant chemotherapy alone for stage III NSCLC after curative surgical anatomical lung resection (pneumonectomy, lobectomy, or segmental resection) were included. Exclusion criteria were (1) patients with stage III disease without N2 status (eg, T4 N0) unless results were reported separately for N2 patients; (2) inconsistency or insufficiency of data to allow valid extraction; (3) any preoperative radiotherapy. Where patients could potentially be included in more than 1 study (registry studies with overlapping dates), results from the larger study were included preferentially; results from the smaller study were used only when a specific outcome was not reported by the larger study.

Data Extraction

Two authors (L.T, L.H.) independently extracted the following data from each source: first author; year of publication; study type; number of subjects; demographics; stage of primary tumor; resection type; chemotherapy regimen; PORT details; mortality outcomes. The primary outcome was overall survival (OS) and the secondary outcome was disease-free survival (DFS), measured from date of surgery to date of death from any cause or date of first relapse, or death without relapse, respectively. Data discrepancy was addressed by these authors and consensus found. Patient consent was not required for this study.

Data Analysis

Meta-analysis was performed in line with recommendations from the Cochrane Collaboration Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Analysis was performed using STATA, version 11.0 (StataCorp, College Station, Tex).

Survival Analysis

Survival was estimated from Kaplan–Meier curves using a recognized practical spreadsheet method.[20] Direct methods were used where data were available; where not possible, indirect methods were used based on summary statistics. Overall pooled estimates and 95% confidence intervals (CIs) of clinical outcomes were analyzed using the risk ratio (RR) and its standard error using a random effects model. The inverse variance method was used. Meta-regression was performed to assess the impact of study characteristics on survival outcomes. The regression coefficient represents the estimated increase in the log hazard ratio (HR) per unit increase in the covariate.

Heterogeneity

Interstudy heterogeneity was explored using the χ^2 statistic, and the I^2 value was calculated to quantify the degree of heterogeneity across trials that could not be attributable to chance alone. Significant heterogeneity was considered to be present when I^2 was more 50%. Further heterogeneity and risk of bias assessment was performed through visual inspection of funnel plots for study outliers (against pseudo 95% CIs), and Egger's test for small study effects.

RESULTS

Eligible Studies

Sixteen studies met the inclusion criteria but 6 were excluded because reported data did not allow extraction of comparison survival outcomes for the groups of interest[21-26] (Figure 1). The 10 remaining studies[27-36] included 3 prospective studies, including 2 randomized controlled

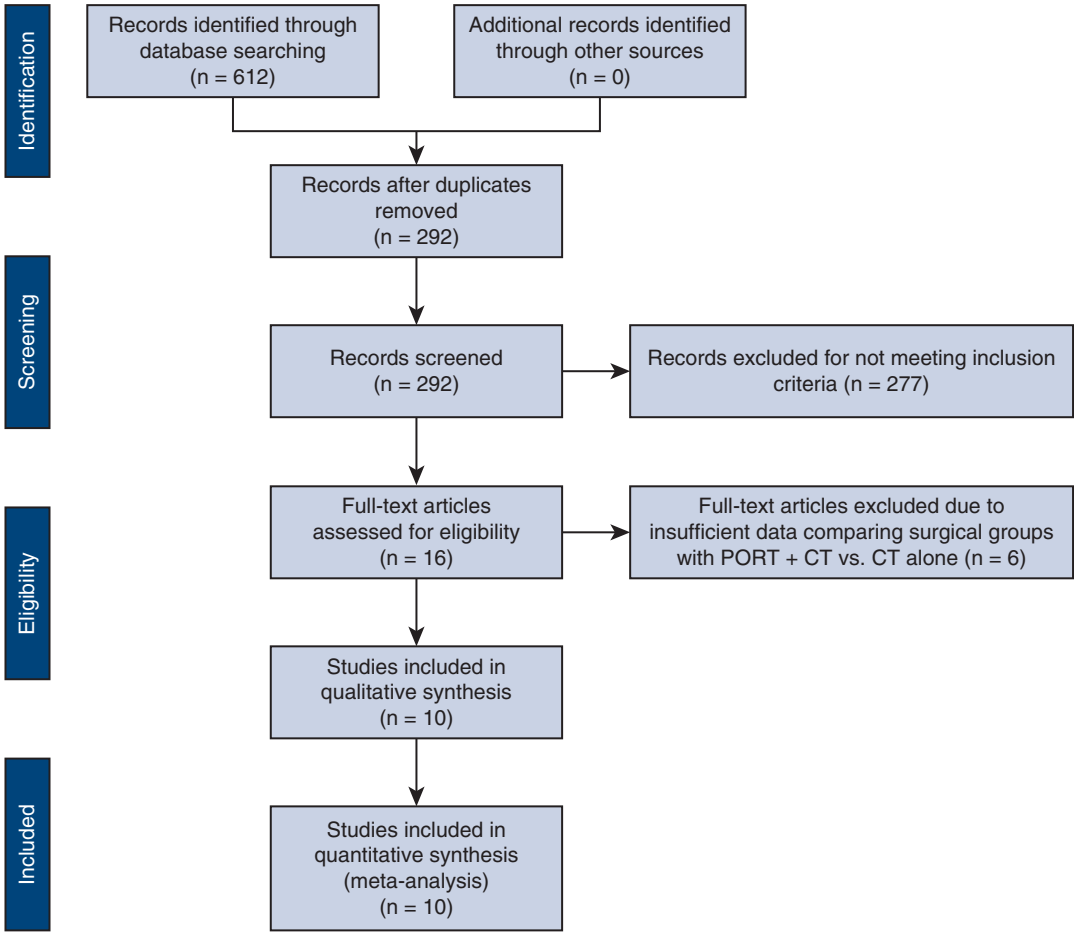


FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for systematic review and study selection. *PORT*, Postoperative radiotherapy; *CT*, chemotherapy.

trials addressing the specific question of this meta-analysis, 4 retrospective studies, and 3 national database analyses, giving a pooled dataset of 18,077 patients (5453 [30.2%] receiving PORT and 12,624 [69.8%] without). Characteristics of included studies are shown in Table 1, with resection type, chemotherapy regimens, and radiotherapy details summarized in Table 2.

Comparison outcomes between PORT and no PORT groups were reported for OS alone in 2 studies[28,29] owing to the mixed inclusion of nonchemotherapy patients for other end points. One study[32] was excluded from OS analysis owing to potential duplication of data from a larger study[28] but included in the analysis of other outcomes not elsewhere reported.

Surgical resection details for PORT and non-PORT groups receiving adjuvant chemotherapy were explicitly reported for 4987 patients across 5 studies.[31,33-36] A total of 428 (8.6%) underwent pneumonectomy; the remainder had more limited resections including lobectomy (3975, 79.7%), wedge or sublobar resection (565, 11.3%), or bilobectomy (19, 0.4%).

Histopathologic subtype was recorded less reliably and less consistently: of those studies reporting by N2 subgroup defined by this meta-analysis, 2 provided full details[31,32] and 2 provided dichotomous groups: squamous or nonsquamous,[35] and adenocarcinoma or nonadenocarcinoma.[36] Summed totals included adenocarcinoma 1577 (61.1%), squamous 601 (23.3%), nonsquamous (including adenocarcinoma) 76 (2.9%), nonadenocarcinoma (including squamous) 111 (4.3%), and others 217 (8.4%).

PORT and no PORT groups were generally well matched across studies with no significant differences in age (standardized mean difference –0.109; $P = .108$), sex (RR, 0.930; $P = .334$), performance status (Eastern Cooperative Oncology Group = 0: RR, 1.193; $P = .407$; Eastern Cooperative Oncology Group = 1: RR, 1.122; $P = .199$), and histopathologic subtype (adenocarcinoma; RR, 1.048; $P = .581$; squamous cell carcinoma RR, 1.060; $P = .319$). Patients receiving PORT were less likely to have undergone pneumonectomy (RR, 0.157; $P = .001$) and more likely to have T3 disease (RR, 1.087; $P = .04$).

TABLE 1. Synopsis of studies

Reference	Study design	Study arms	n	Median age (range)	Sex M:F	Reported outcomes
Cao et al, 2015[27] 2008-2009 China	Single center nonrandomized retrospective *Propensity matched +/–N1	No PORT PORT	102 38	Not stated	105:69*	5-y OS: 28.8% 5-y DFS: 17.4% 5-y OS: 39.5% 5-y DFS: 25.0%
Corso et al, 2015[28] 1998-2006 US	National database retrospective	No PORT PORT	5319 1660	Not stated	Not stated	5-y OS: 33.6% 5-y OS: 36.7%
Dai et al, 2011[29] 2003-2005 China	Single-center nonrandomized retrospective	No PORT PORT	100 61	60 (27-79)*	83:42* 77:19*	5-y OS: 31.9% median OS: 33.1 mo 5-y OS: 38.2% median OS: 48.3 mo
Douillard et al, 2008[30] 1994-2000 France/Spain/Italy	Multicenter nonrandomized prospective	No PORT PORT	70 48	59 (18-75)*	86%:14%*	5-y OS: 34.0% median OS: 23.8 mo 5-y OS: 47.4% median OS: 47.4 mo
Kim et al, 2014[31] 2000-2011 South Korea	Single-center nonrandomized retrospective *Propensity matched	No PORT PORT	111 38	60 (34-84)	70:41 29:9	5-y OS: 58.2% 5-y DFS: 31.0% 5-y OS: 49.9% 5-y DFS: 38.4%
Mikell et al, 2015[32] 2004-2006 US	National database retrospective *Propensity matched	No PORT PORT	1197 918	62 (30-84) 65 (27-89)	550:647 441:477	5-y OS: 34.7% median OS: 38 mo 5-y OS: 39.8% median OS: 42 mo
Perry et al, 2007[33] 1998-2000 US	Single-center randomized prospective	No PORT PORT	18 19	61 (40-78) 66 (48-78)	13:5 12:7	1-y OS: 72% median OS: 33.2 mo 1-y OS: 74% median OS: 41.5 mo
Robinson et al, 2015[34] 2006-2010 US	National database retrospective	No PORT PORT	2633 1850	66 (27-89) 64 (19-89)	1266:1367 868:982	5-y OS: 34.8% median OS: 40.7 mo 5-y OS: 39.3% median OS: 45.2 mo
Shen et al, 2014[35] 2004-2009 China	Multicenter randomised prospective	No PORT PORT	69 66	60 (35-74) 58 (37-72)	45:24 43:23	5-y OS: 27.5% median OS: 28 mo 5-y OS: 37.9% median OS: 40 mo
Zou et al, 2010[36] 1998-2005 China	Multicenter nonrandomized retrospective	No PORT PORT	79 104	61 (26-75)	55:24 74:30	5-y OS: 22.2% 5-y OS: 30.5%

M, Male; *F*, female; *PORT*, postoperative radiotherapyl; *OS*, overall survival; *DFS*, disease-free survival. *Results of broader study group, not reported specifically for patients receiving N2 chemotherapy +/– PORT.

Primary End Points

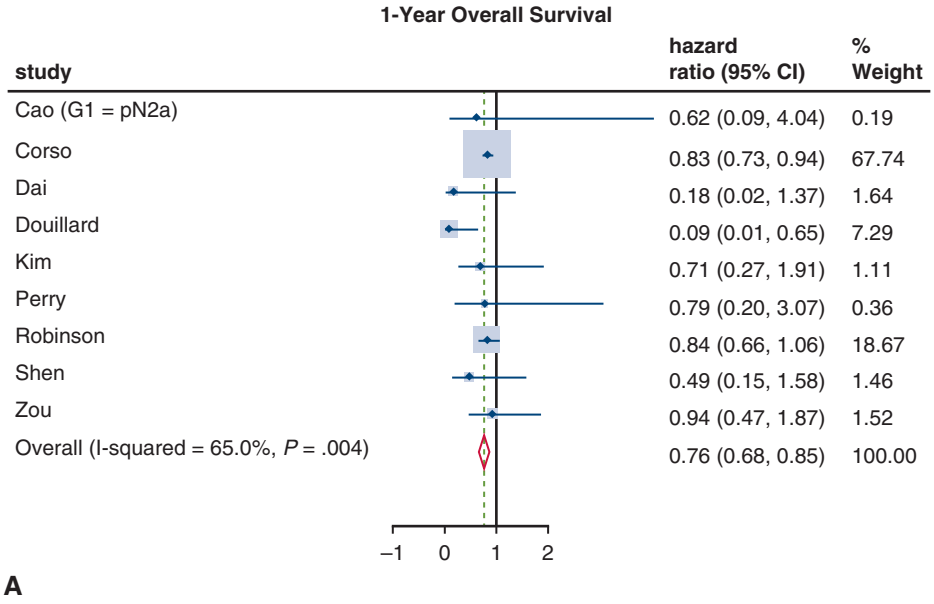
Overall survival. All studies provided Kaplan–Meier estimates of OS comparing PORT with no PORT. Median OS ranged from 23.8 to 72.0 months in the no-PORT group and from 36.0 to 59.5 months in the PORT group. PORT significantly improved OS at 1 year (n = 18,077; HR, 0.768; 95% CI, 0.687-0.849; $P < .0001$), 3 years (n = 18,077; HR, 0.914; 95% CI, 0.866-0.962; $P < .0001$), and 5 years (n = 18,040; HR, 0.898; 95% CI, 0.854-0.941; $P < .0001$) (Figure 2). Interstudy heterogeneity was high at 1 year (I^2 60.8%, $P = .006$) and low at 3 (I^2 0.0%, $P = .624$) and 5 years (I^2 0.0%, $P = .611$) (Table 3).

Disease-free survival. Five studies provided Kaplan–Meier estimates of DFS comparing PORT with no PORT.[27,31,33,35,36] Median DFS ranged from 16.8 to 25.5 months in the no-PORT groups and 25.8 to 33.7 months in the PORT groups. PORT significantly improved DFS at 1 year (n = 676; HR, 0.733; 95% CI, 0.414-1.052, $P < .0001$), 3 years (n = 676; HR, 0.732; 95% CI,

TABLE 2. Treatment details

Study	Surgical resection	Chemotherapy regimen	Radiotherapy regimen
Cao et al[27]	Pneumonectomy 11.9% Lobectomy 53.2% Bilobectomy 8.3% Wedge resection 6.4% (includes 34 patients excluded from meta-analysis)	Carboplatin (AUC5) or cisplatin (75 mg/m^2) with vinorelbine (25 mg/m^2) or paclitaxel (200 mg/m^2) or gemcitabine (1250 mg/m^2) for 4-6 cycles	50.4 Gy in 28 fractions 3D conformal
Corso et al[28]	Not specified for IIIA N2, chemotherapy +/– PORT patients	Not specified for IIIA N2, chemotherapy +/– PORT patients	Varied: categorized as 45-54 Gy, >54-60 Gy, and >60 Gy 3D conformal and IMRT
Dai et al[29]	Pneumonectomy 10.0% (12 PORT; 10 no PORT) Lobectomy 90.0% (84 PORT; 115 no PORT) (includes 60 patients excluded from meta-analysis)	Cisplatin or paclitaxel-based regimen for median 4 cycles	60 Gy in 30 fractions 2D (55) and 3D conformal (41)
Douillard et al[30]	Pneumonectomy 36.9% (90 PORT; 220 no PORT) Other resection 63.1% (142 PORT; 388 no PORT) (includes 722 patients excluded from meta-analysis)	Cisplatin (100 mg/m^2 d1) + Vinorelbine (30 mg/m^2 d1, d8, d15, d22) for maximum 4 cycles	45-60 Gy in 25-30 fractions Modality not specified
Kim et al[31]	Pneumonectomy 8.7% (1 PORT; 12 no PORT) Bilobectomy 10.7% (7 PORT; 9 no PORT) Lobectomy 80.5% (30 PORT; 90 no PORT)	Carboplatin/paclitaxel or cisplatin with vinorelbine, paclitaxel or gemcitabine for median 4 cycles*	50-56 Gy (median 54 Gy) at 1.8-2.0 Gy per fraction 2D (14) and 3D conformal (27)
Mikell et al[32]	Not specified for IIIA N2, chemotherapy +/– PORT patients	Not specified for patients with IIIA N2, chemotherapy +/–PORT†	Varied: categorized as <50 Gy, 50-60 Gy, and >60 Gy 3D conformal
Perry et al[33]	Pneumonectomy 21.6% (3 PORT; 5 no PORT) Bilobectomy: 8.1% (3 PORT) Lobectomy 70.3% (13 PORT; 13 no PORT)	Carboplatin AUC6 + paclitaxel 200 mg/m^2 for median 4 cycles	50 Gy in 25 fractions Modality not stated
Robinson et al[34]	Pneumonectomy 8.3% (108 PORT; 262 no PORT) Lobectomy 79.9% (1439 PORT; 2109 no PORT) Sublobar 12.6% (303 PORT; 262 no PORT)	Single agent 4.2% 78 PORT, 95 no PORT Combination 95.8% 1637 PORT, 2278 no PORT	45-82.8 Gy (median 54 Gy, 17.7% >60 Gy) Modality not stated
Shen et al[35]	Pneumonectomy 27.4% (18 PORT; 19 no PORT) Lobectomy 72.4% (48 PORT; 50 no PORT)	Cisplatin (60 mg/m^2) with paclitaxel (175 mg/m^2) for 4 cycles	50.4 Gy in 28 fractions 3D conformal
Zou et al[36]	All lobectomy	Cisplatin (40 mg/m^2 IV d1-3) with Etoposide (60 mg/m^2 IV d1-3) or gemcitabine (1000 mg/m^2 d1 and d8) or Paclitaxel (135 mg/m^2 IV d1) for median 4 cycles	48-54 Gy (median 50 Gy) in 1.8-2 Gy fractions 2D (29) and 3D conformal (75)

PORT, Postoperative radiotherapy; *3D*, 3-dimensional; *IMRT*, intensity-modulated radiation therapy; *IV*, intravenous. *A total of 41 patients received induction chemotherapy, mainly cisplatin/paclitaxel (median 2 cycles; range 2-4). †>9.1% (maximally 18.2%) patients received unspecified induction chemotherapy.



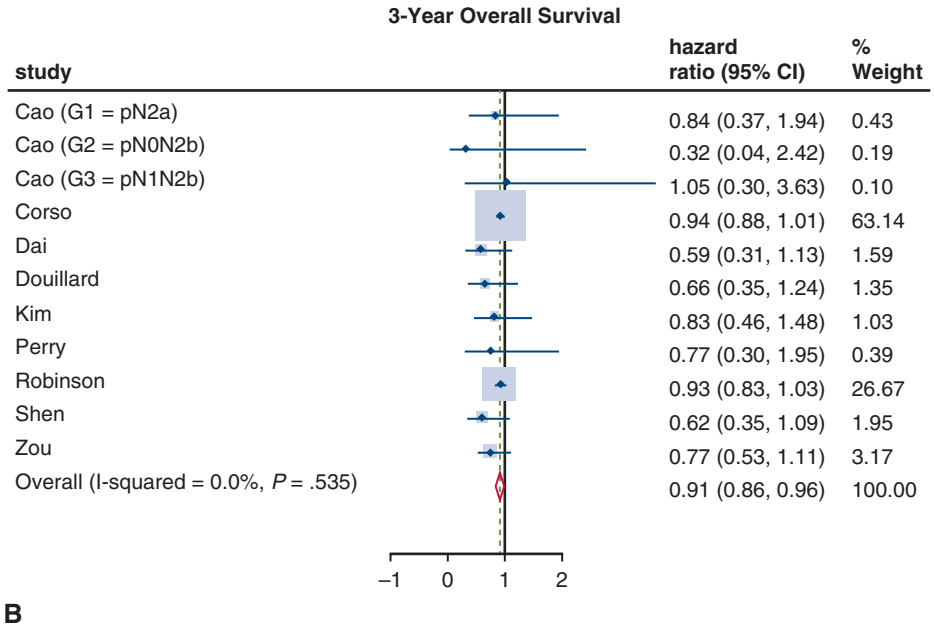


FIGURE 2. Forest plot for overall survival at 1, 3, and 5 years with PORT and no PORT in patients with stage IIIA N2 non–small cell lung cancer. Individual study and pooled HRs are shown with 95% CIs. Overall survival at 1, 3, and 5 years was significantly greater with PORT compared with no PORT. A, 1-year HR, 0.768; 95% CI, 0.687-0.849; $P < .0001$. B, 3-year HR, 0.914; 95% CI, 0.866-0.962; $P < .0001$. C, 5-year HR, 0.898; 95% CI, 0.854-0.941; $P < .0001$. *CI*, Confidence interval; *HR*, hazard ratio.

0.566-0.898; $P < .0001$) and 5 years (n = 639; HR, 0.735; 95% CI, 0.589-0.880; $P < .0001$). Interstudy heterogeneity was zero at 1 and 3 years (I^2 0.0%, 0.1%, respectively) and mild at 5 years (I^2 38.4%, $P = .150$) (Table 3).

Meta-regression. Meta-regression was used to determine any effect of patient characteristics on survival outcomes according to receipt of PORT or not. Characteristics analyzed included age, sex, T stage, surgical resection type, extent of N2 disease (single-station vs multistation), histopathologic subtype, and performance status. No significant effect was seen on OS or DFS for any study characteristic analyzed at 1, 3, or 5 years.

Heterogeneity assessment and bias exploration. Funnel plots were visually inspected for outliers to assess for publication bias and no asymmetry was detected for OS or DFS. Egger's test for small study effects was performed for each outcome. No significant small study effects were observed for DFS at 1, 3, or 5 years ($P = .822$, .877, and .833,

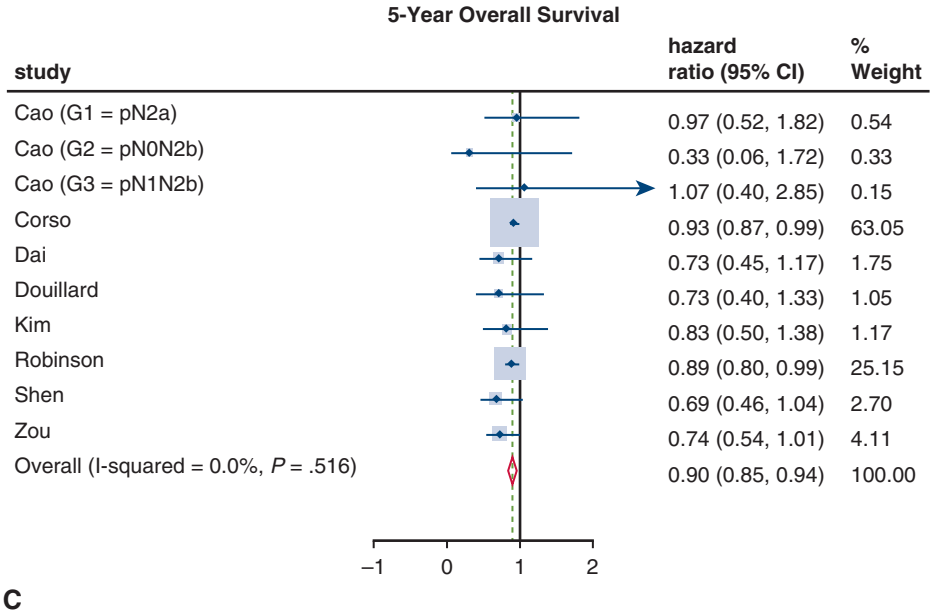


FIGURE 2. *(Continued).*

respectively) or OS ($P = .053$) at 1 year; a significant small study effect was seen for OS at 3 and 5 years ($P = .002$ and $P = .013$, respectively).

DISCUSSION

Operable stage IIIA disease forms a subgroup of locally advanced lung cancer where many options for management exist but best practice is not fully determined. This meta-analysis lends weight to the suggestion that PORT following standard adjuvant chemotherapy for patients with completely resected N2 disease increases both DFS and OS. PORT likely improves local control by ablation of micrometastatic disease within unresected mediastinal nodes. Prevention of local recurrence may be the mechanism whereby long-term OS is demonstrably improved and should be considered in the perioperative planning of such patients.

Before mandating radiotherapy for all, it is important to consider that trimodality treatment may be associated with increased complications, particularly in patients with limited respiratory reserve, and to acknowledge that the results of this meta-analysis must be interpreted with some caution owing to limitations of the data included. Patients who undergo pneumonectomy have greater mortality rates after chemoradiotherapy than patients with less-extensive resection, primarily due to respiratory toxicity,[37] and indeed there is a cohort of surgeons who consider the need for pneumonectomy a contraindication to surgery in N2 disease.[38] Only a small proportion of patients included in this meta-analysis underwent pneumonectomy or bilobectomy, limiting the ability to draw inferences on the effect of radiotherapy according to type of surgery. Quality of life must also be given consideration alongside survival effect: disabling breathlessness may develop after radiotherapy in patients with insufficient postoperative respiratory function. Extensive preoperative assessment including evaluation of performance status, full lung volume, and functional testing should be performed to

TABLE 3. Results of survival analysis

		Overall effect				Heterogeneity assessment		
	Number of studies	Hazard ratio	95% LCI	95% UCI	*P* value	χ^2	*P* value	I^2
Overall survival								
1 y	9	0.77	0.68	0.85	<.0001	22.83	.004	65.0
3 y	9	0.91	0.86	0.96	<.0001	8.97	.535	0.0
5 y	8	0.90	0.85	0.94	<.0001	8.18	.516	0.0
Disease-free survival								
1 y	5	0.73	0.41	1.05	<.0001	0.736	.736	0
3 y	5	0.73	0.57	0.90	<.0001	6.01	.422	0.10
5 y	4	0.73	0.59	0.88	<.0001	8.12	.150	38.4

LCI, Lower confidence interval; *UCI*, upper confidence interval.

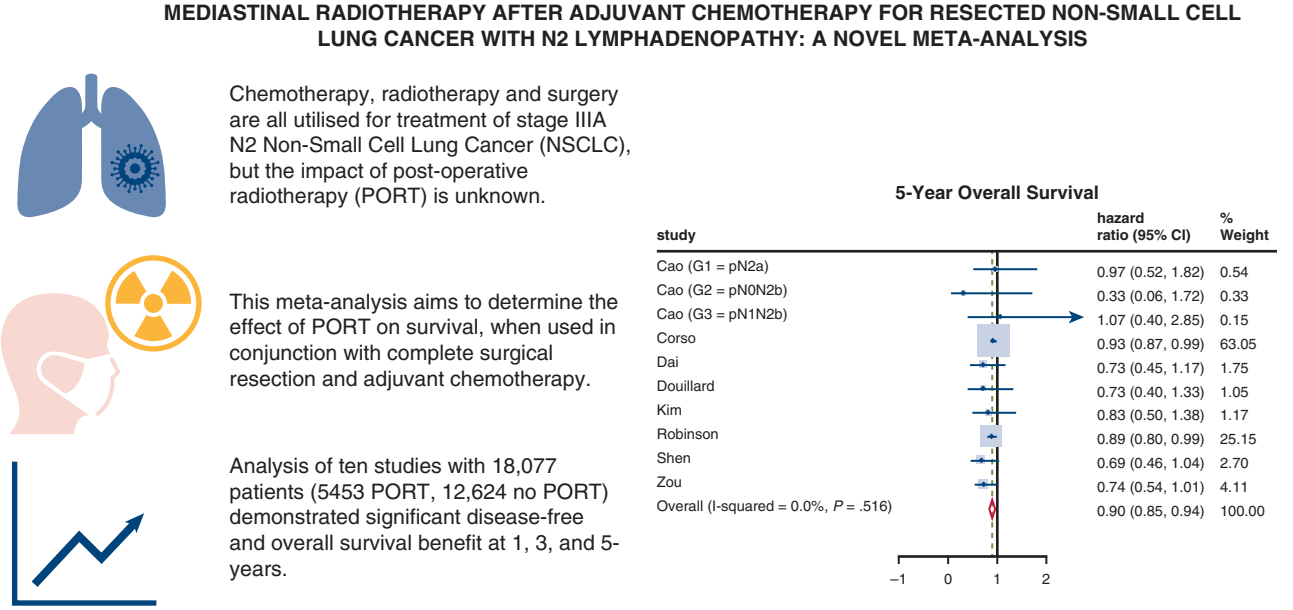


FIGURE 3. Summary of study objectives, design, and outcome. *CI*, Confidence interval.

optimize selection of appropriate surgical candidates and determine those most likely to benefit from PORT.[39]

The role of adjuvant radiotherapy for patients who are N2 stage IIIA after chemotherapy was not the specific focus of most papers included within this meta-analysis, meaning relevant data were extracted from summary statistics and were not necessarily uniform across papers. For example, the large database studies provide the majority of patients for analysis in terms of survival outcomes but by design cannot provide granular detail of patient characteristics or treatments received.

The allocation of PORT was randomized in only 2 of the smaller studies,[33,35] both terminating early owing to slow recruitment and including merely 172 patients. One further prospective study[30] was randomized but by adjuvant chemotherapy allocation, not radiotherapy, which was given at physician's discretion. Although most nonrandomized studies did not demonstrate significant differences in patient characteristics between PORT and no-PORT groups, that alone does not exclude bias: fitter patients, patients with more extensive N2 disease, less complete nodal resection, or particular histology may be more likely to receive PORT, each a factor that could have a notable effect on OS or DFS.

Details of radiotherapy dose, planning techniques, and even successful completion or not are sparse: in 1 study[33] just 14 of 19 patients achieved the planned dose. Although most papers here are more recent than those studies that demonstrated negative results in early-stage disease and equivocal results in node-positive disease, many patients were nonetheless planned using 2-dimensional or conformal 3-dimensional techniques with nonstandardized fields, sometimes including elective supraclavicular nodal irradiation, which have a lower therapeutic index than current inverse planning methods.[40]

The chemotherapy regimens used were varied and, in some cases, would be considered less effective than currently employed treatments. Furthermore, where detailed, staging did not necessarily include positron emission tomography imaging and surgery did not include full lymph node dissection. Given the multicenter nature of the included studies, there was no standardization in the staging of included patients (indeed, no studies described the methodology of lymphadenectomy or pathologic staging), and variability in staging could result in inclusion of some patients with micrometastatic contralateral mediastinal or supraclavicular (both N3) disease, both conferring a poorer prognosis than stage IIIA disease.

Although we did not find a significant impact on survival outcomes when performing metaregression for resection type, T stage, histopathologic subtype or performance status, the small number of patients in some subcategories may well be underpowered to detect true differences.

There may be differing roles for adjuvant radiotherapy after chemotherapy when N2 disease is detected incidentally in the lymph node dissection rather than when detected preoperatively, particularly if there has been appropriate staging in the former situation, but only one study gave such details, being limited to patients with occult N2 disease only.[33] Incidental disease persisting in nodes after neoadjuvant chemotherapy may have a different natural history to incidental disease found following surgery as first treatment. To reach as clear a result as possible, our meta-analysis aimed to include a homogeneous population: less

than 3% received any preoperative chemotherapy, a proportion thought unlikely to significantly affect outcomes.

Patients with bulky or multistation disease have poorer survival than those with single-station disease,[41] and multistation N2 disease is more powerfully associated with poor prognosis than concomitant involvement of N1 nodes,[42] findings confirmed in the 3 studies here, which detailed the extent of N2 involvement. This meta-analysis has not determined whether the benefit of PORT extends across all patients with N2 disease or is limited to a smaller group, potentially those patients at greater risk with multistation disease, as relatively few studies provided this information.

These results specifically address the question of whether PORT confers a survival advantage after chemotherapy in patients who have undergone R0 resection with stage IIIA N2 disease. We cannot comment on quality of life issues and cannot determine whether chemotherapy and radiotherapy are best delivered ahead of surgery or as adjuvant treatment or whether best delivered sequentially or concurrently.

CONCLUSIONS

Patients with NSCLC and stage IIIA N2 disease comprise a heterogeneous population. Improvements in staging accuracy and surgical techniques have improved the selection of patients for curative resection and adjuvant chemotherapy has become standard treatment. This study demonstrates a significant DFS and OS benefit from the addition of PORT (Figure 3). In light of these findings, we advocate the consideration of PORT after chemotherapy for all such patients following specialist multidisciplinary assessment and comprehensive discussion of the benefits and risks of treatment.

Given the apparent survival benefit seen with PORT here and the described limitations of predominantly retrospective data, further prospective research is essential. The phase III trial LungART is the largest randomized trial to specifically address the question of PORT after resected N2 NSCLC, although (neo)adjuvant chemotherapy was not mandated but widely used. Preliminary results indicate a significant improvement in local control, with nonsignificant DFS benefit at the expense of toxicity driven predominantly by increased cardiorespiratory morbidity and death as a first DFS event giving no measurable difference in OS.[43] Further results will provide valuable information on the role of modern radiotherapy, including prospectively collected quality of life parameters and the assessment of patient-specific data and radiotherapy planning data to determine which factors offset the benefit of local disease control. Patients with insufficient nodal resection or with extracapsular nodal spread were excluded from the LungART trial and may be those most likely to benefit from PORT to the magnitude described within this meta-analysis.

Conflict of Interest Statment

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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