

# Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial



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## Summary

**Background** Results from phase II studies in patients with stage IIIA non-small-cell lung cancer with ipsilateral mediastinal nodal metastases (N2) have shown the feasibility of resection after concurrent chemotherapy and radiotherapy with promising rates of survival. We therefore did this phase III trial to compare concurrent chemotherapy and radiotherapy followed by resection with standard concurrent chemotherapy and definitive radiotherapy without resection.

**Methods** Patients with stage T1-3pN2M0 non-small-cell lung cancer were randomly assigned in a 1:1 ratio to concurrent induction chemotherapy (two cycles of cisplatin [50 mg/m<sup>2</sup> on days 1, 8, 29, and 36] and etoposide [50 mg/m<sup>2</sup> on days 1–5 and 29–33]) plus radiotherapy (45 Gy) in multiple academic and community hospitals. If no progression, patients in group 1 underwent resection and those in group 2 continued radiotherapy uninterrupted up to 61 Gy. Two additional cycles of cisplatin and etoposide were given in both groups. The primary endpoint was overall survival (OS). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00002550.

**Findings** 202 patients (median age 59 years, range 31–77) were assigned to group 1 and 194 (61 years, 32–78) to group 2. Median OS was 23·6 months (IQR 9·0–not reached) in group 1 versus 22·2 months (9·4–52·7) in group 2 (hazard ratio [HR] 0·87 [0·70–1·10]; p=0·24). Number of patients alive at 5 years was 37 (point estimate 27%) in group 1 and 24 (point estimate 20%) in group 2 (odds ratio 0·63 [0·36–1·10]; p=0·10). With N0 status at thoracotomy, the median OS was 34·4 months (IQR 15·7–not reached; 19 [point estimate 41%] patients alive at 5 years). Progression-free survival (PFS) was better in group 1 than in group 2, median 12·8 months (5·3–42·2) vs 10·5 months (4·8–20·6), HR 0·77 [0·62–0·96]; p=0·017; the number of patients without disease progression at 5 years was 32 (point estimate 22%) versus 13 (point estimate 11%), respectively. Neutropenia and oesophagitis were the main grade 3 or 4 toxicities associated with chemotherapy plus radiotherapy in group 1 (77 [38%] and 20 [10%], respectively) and group 2 (80 [41%] and 44 [23%], respectively). In group 1, 16 (8%) deaths were treatment related versus four (2%) in group 2. In an exploratory analysis, OS was improved for patients who underwent lobectomy, but not pneumonectomy, versus chemotherapy plus radiotherapy.

**Interpretation** Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) non-small-cell lung cancer.

**Funding** National Cancer Institute, Canadian Cancer Society, and National Cancer Institute of Canada.

## Introduction

Patients with stage IIIA non-small-cell lung carcinoma with clinically evident, ipsilateral mediastinal nodal metastases (N2) had poor outcomes after treatment with surgical resection or radiotherapy.<sup>1–4</sup> Addition of chemotherapy to radiotherapy significantly improved survival for patients in this disease-stage subset and is now regarded as standard care.<sup>5–8</sup> In subsequent phase III trials, survival was much better with concurrent chemotherapy and radiotherapy than with sequential administration.<sup>9–11</sup>

Phase II pilot studies were done to test the role of surgical resection after induction treatment with chemotherapy alone or concurrent chemotherapy and radiotherapy to optimise local control after systemic treatment. The results were controversial, with long-term

survival rates that were higher than expected.<sup>11–13</sup> However, substantial toxicity, postoperative morbidity, and mortality were noted, and the findings of these studies were criticised because the patients enrolled had heterogeneous substages of disease and seemed unusually healthy compared with the general population with stage III disease.

On the basis of the findings of two previous phase II studies done by the Southwest Oncology Group,<sup>14,15</sup> we designed a phase III trial (National Cancer Institute numbers R9309, INT0139) in which patients with pathologically documented stage IIIA(pN2) non-small-cell lung cancer were given concurrent chemotherapy plus radiotherapy followed by surgery, versus chemotherapy with definitive radiotherapy and without surgery. The objectives were to assess whether resection resulted

Lancet 2009; 374: 379–86

Published Online

July 27, 2009

DOI:10.1016/S0140-6736(09)60737-6

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in a significant improvement in survival outcomes compared with just chemotherapy plus radiotherapy; examine the toxicity in each group; and report patterns of local and distant disease recurrence.

## Methods

### Patients

The study was done at multiple academic and community hospitals in the USA and Canada. The international system was used to stage lung cancer,<sup>1</sup> using a CT scan of the chest, liver, and adrenal glands; bone scan; and CT or MRI scan of the brain. Inclusion criteria were stage IIIA(pN2) disease: T1, T2, or T3 primary non-small-cell lung cancer with pathological proof of N2 involvement (from biopsy samples of ipsilateral mediastinal nodes that were visible on radiographs by any of several protocol-specified standard procedures). If contralateral mediastinal nodes that were larger than 1 cm were visible on the CT scan, a biopsy was needed to exclude N3 (stage IIIB) disease.

Patients were assessed by a thoracic surgeon, radiation oncologist, and medical oncologist (each approved to participate through a centralised questionnaire process) to establish that N2 disease was present to the extent that concurrent chemotherapy and radiotherapy was regarded as the standard approach instead of definitive resection, and that the cancer was potentially technically resectable. Pulmonary function criteria were mandated by the protocol (standard formula specified in protocol: predicted postresection forced expiratory volume in 1 s

[FEV<sub>1</sub>] of at least 800 cm<sup>2</sup> on quantitative perfusion scan if FEV<sub>1</sub> overall was less than 2000 cm<sup>3</sup>). Pulmonary medicine specialists were also consulted as needed to confirm pulmonary fitness for a potential resection. The Karnofsky performance status was 90 or 100; or, if 70 or 80, the albumin was at least 85% of the normal value with less than 10% weight loss within the previous 3 months.

All patients provided written informed consent after study approval by a local institutional review board.

### Study design

We stratified eligible patients by primary T designation (T1 vs T2 vs T3), Karnofsky performance status (90 or 100 vs 70 or 80), and contralateral mediastinal nodal sampling (yes vs no). Patients were randomly assigned in an unmasked manner to induction chemotherapy plus radiotherapy followed by surgery (group 1), or the same induction chemotherapy and radiotherapy with completion of definitive-dose radiotherapy (group 2). The random allocation schedule was generated by computer at the Radiation Therapy Oncology Group statistical centre, whose personnel were not associated with the institutions or investigators. The induction chemotherapy was two cycles of cisplatin (50 mg/m<sup>2</sup> on days 1, 8, 29, and 36, intravenous infusions) and etoposide (50 mg/m<sup>2</sup> on days 1–5 and 29–33, intravenous infusions); and induction thoracic radiotherapy (45 Gy) was administered beginning on day 1 in 1.8 Gy daily fractions. We reassessed disease status with CT scan plus repeat pulmonary function tests 2–4 weeks after patients completed radiotherapy in group 1, and 7 days before they completed induction chemotherapy plus radiotherapy in group 2. If disease had not progressed and the patient remained medically healthy, we did a complete surgical resection (with protocol-specified mediastinal lymph node sampling or dissection) 3–5 weeks after completion of radiotherapy in group 1, or the radiation dose was continued to 61 Gy without interruption in group 2. We gave patients two cycles of consolidation chemotherapy (same doses and schedule as during induction). Dose reduction guidelines were specified in the protocol for chemotherapy plus radiotherapy, with central quality control.

Patients were scheduled to have a chest CT scan 4–6 weeks after completion of the last chemotherapy cycle. Patients were followed up every 2 months for 1 year, every 3 months for 2 years, and then every 6 months indefinitely. CT scans of the thorax and upper abdomen, and MRI or CT scan of the brain were done at 12 months, 18 months, and 24 months, and every year thereafter.

### Statistical analysis

We used Zelen's randomised permuted block within strata to assign patients to a treatment group.<sup>16</sup> Analyses were by intention to treat, using only eligible patients as

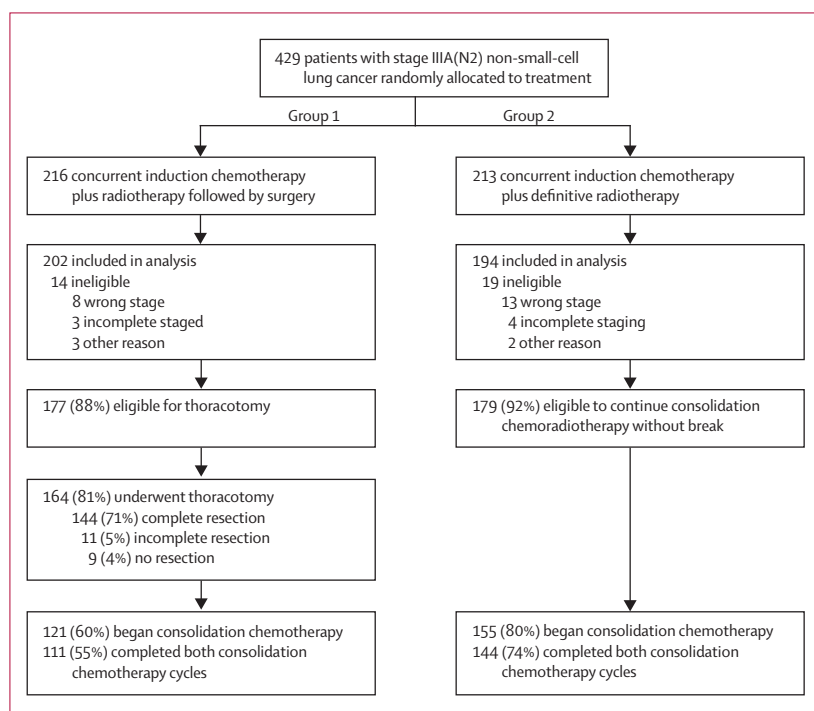


Figure 1: Trial profile

N2=ipsilateral mediastinal nodal metastases.

	CT/RT/S (group 1, n=202)	CT/RT (group 2, n=194)	Total (n=396)
<b>Age (years)</b>			
Median (range)	59 (31–77)	61 (32–78)	60 (31–78)
≤60	113 (56%)	95 (49%)	208 (53%)
>60*	89 (44%)	99 (51%)	188 (47%)
<b>Sex</b>			
Men	131 (65%)	121 (62%)	252 (64%)
Women	71 (35%)	73 (38%)	144 (36%)
<b>Karnofsky performance status</b>			
70–80	23 (11%)	25 (13%)	48 (12%)
90–100	179 (89%)	169 (87%)	348 (88%)
<b>Estimated weight loss in past 6 months (kg)</b>			
<5	154 (76%)	146 (75%)	299 (76%)
5–10	36 (18%)	30 (15%)	67 (17%)
>10	7 (3%)	10 (5%)	17 (4%)
Unknown	5 (2%)	8 (4%)	13 (3%)
<b>Lactate dehydrogenase</b>			
Normal	148 (73%)	147 (76%)	295 (74%)
Abnormal†	39 (19%)	33 (17%)	72 (18%)
Not done	15 (7%)	14 (7%)	29 (7%)
<b>Histology</b>			
Squamous cell carcinoma	64 (32%)	65 (34%)	129 (33%)
Adenocarcinoma	79 (39%)	82 (42%)	161 (41%)
Large cell	29 (14%)	24 (12%)	53 (13%)
Mixed/other NSCLC	30 (15%)	23 (12%)	53 (13%)
<b>T stage</b>			
T1	50 (25%)	47 (24%)	97 (24%)
T2	130 (64%)	121 (62%)	251 (63%)
T3	22 (11%)	26 (13%)	48 (12%)
<b>Number of positive nodal stations reported‡</b>			
1	153 (76%)	146 (75%)	299 (76%)
2	39 (19%)	39 (20%)	78 (20%)
3	4 (2%)	4 (2%)	8 (2%)
Unknown	6 (3%)	5 (3%)	11 (3%)

Data are number (%), unless otherwise indicated. CT=chemotherapy. RT=radiotherapy. S=surgery. NSCLC=non-small-cell lung cancer. \*63 (16%) patients were at least 70 years of age. †Greater than institutional upper limit of normal. ‡Not all patients had mediastinoscopy, since method of recording disease with ipsilateral mediastinal nodal metastases was at the discretion of the investigator.

Table 1: Baseline characteristics of eligible patients

per Radiation Therapy Oncology Group policy. The primary endpoint was overall survival (OS), defined as time from randomisation to death from any cause. Secondary endpoints were progression-free survival (PFS), defined as time from randomisation to disease progression, detection of a secondary primary tumour, or death from any cause; toxicity; and patterns of failure.

We calculated the sample size using a non-stationary Markov process to model survival with the Lakatos method,<sup>17</sup> assuming a one-sided log-rank test with a type I error rate of 0·05 and 93% statistical power, and

	CT/RT/S (group 1, n=202)			CT/RT (group 2, n=194)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Leucopenia	82 (41%)	15 (7%)	0	76 (39%)	31 (16%)	0
Neutropenia	54 (27%)	23 (11%)	0	47 (24%)	33 (17%)	0
Anaemia	25 (12%)	1 (<1%)	0	42 (22%)	5 (3%)	0
Thrombocytopenia	10 (5%)	4 (2%)	0	12 (6%)	11 (6%)	0
Worst haematological toxicity per patient	89 (44%)	28 (14%)	0	75 (39%)	50 (26%)	0
Nausea or emesis, or both	27 (13%)	2 (1%)	0	22 (11%)	4 (2%)	0
Neuropathy	10 (5%)	0	0	4 (2%)	3 (2%)	0
Oesophagitis*	17 (8%)	3 (1%)	0	37 (19%)	7 (4%)	0
Stomatitis or mucositis, or both	6 (3%)	0	0	4 (2%)	1 (<1%)	0
Pulmonary	17 (8%)	1 (<1%)	13 (6%)	24 (12%)	4 (2%)	3 (2%)
Other gastrointestinal or renal	6 (3%)	4 (2%)	0	5 (3%)	2 (1%)	0
Cardiac	4 (2%)	3 (1%)	3 (1%)†	7 (4%)	2 (1%)	0
Miscellaneous infection	5 (2%)	1 (<1%)	0	8 (4%)	0	0
Haemorrhage	0	0	1 (<1%)	0	1 (<1%)	0
Fatigue	11 (5%)	0	0	9 (5%)	0	0
Anorexia	3 (1%)	0	0	4 (2%)	3 (2%)	0
Allergy	1 (<1%)	0	0	3 (2%)	0	0

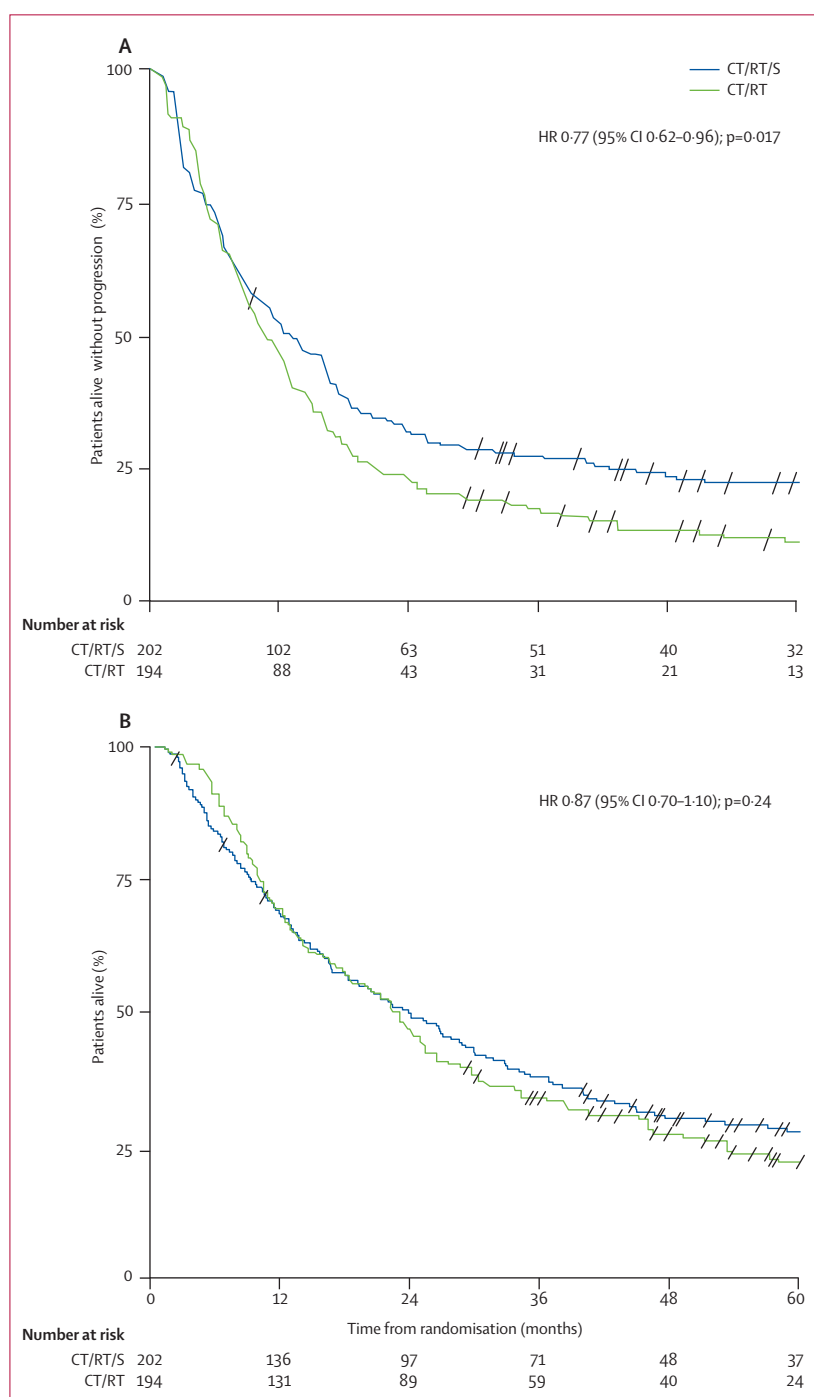
CT=chemotherapy. RT=radiotherapy. S=surgery. \*Only toxicity that was significantly (p=0·0006) different between groups 1 and 2. †One patient also included in grade 5 pulmonary toxicity.

Table 2: Overall worst toxicities

minimum follow-up of 2·5 years. Only two-sided p values are reported. Two interim analyses were specified and done by the independent data safety monitoring board after 33% and 67% of patients were followed up for at least 2·5 years.

The target sample size was 612 (556 eligible) patients to record 507 deaths to detect a 10% absolute improvement in the surgical group, assuming 25% 2-year OS with chemotherapy plus radiotherapy. The size was recalculated after recommendation by the Data Safety and Monitoring Committee, because of slower accrual than projected and updated survival rates from the two phase II trials that represented each group.<sup>14,15</sup> The revised sample size was 510 (484 eligible) patients.

We analysed OS and PFS with the log-rank test, and used the Cox proportional hazards model for multivariate analyses.<sup>18</sup> The adjusted  $\alpha$  at the final analysis was 0·0487. Only the unadjusted estimates and CIs are reported here because the largest difference (between unadjusted and adjusted) was 0·002 for hazard ratios (HRs) and 0·04 for rates of OS and PFS. All figures show Kaplan-Meier estimates.<sup>19</sup> We used stepwise selection in Cox modelling, including sex, weight loss (<5 kg or >5 kg), number of positive nodal stations (1 or 2·3), T stage (T1 vs T2 vs T3), histology (non-squamous vs squamous), age (<60 years vs >60 years), Karnofsky performance status (90 or 100 vs 70 or 80), and lactate dehydrogenase level (normal vs abnormal). We did exploratory logistic regression for factors associated with 5-year survival.



**Figure 2: Progression-free survival (A) and overall survival (B) of intention-to-treat population**  
 Slash marks represent censored results. CT/RT/S=chemotherapy plus radiotherapy followed by surgery (group 1, n=202). CT/RT=chemotherapy plus radiotherapy (group 2, n=194). HR=hazard ratio.

An unplanned, exploratory OS analysis was added for hypothesis generation, prompted by unexpectedly high postoperative mortality rates. Patients in group 1 who underwent pneumonectomy were matched 1:1 with those in group 2 according to age ( $\pm 5$  years), sex, Karnofsky performance status (70 or 80, and 90 or 100),

and clinical T stage (exact match). Patients in group 1 who had a lobectomy were matched 1:1 with those in group 2 according to the same characteristics.

This study is registered with ClinicalTrials.gov, number NCT00002550.

### Role of the funding source

The sponsor had no role in data analysis, writing the report, or the decision to submit for publication. The Radiation Therapy Oncology Group was responsible for data gathering and analysis. The corresponding author with the Radiation Therapy Oncology Group had responsibility for the decision to submit for publication.

### Results

Patient accrual period was from March, 1994, until the end of November, 2001. Because of the extended accrual period resulting in sufficient events, the Data Safety and Monitoring Committee (with knowledge of the survival curves in each group) recommended closure when 429 patients were randomly assigned. A PFS analysis and initial OS have been previously presented, with a subsequent update.<sup>20,21</sup> Definitive estimates are now available for all endpoints; median follow-up for all patients was 22.5 months (range 0.9–125.1) and for those still alive at the final analysis was 69.3 months (6.2–125.1).

Figure 1 shows the trial profile; 396 (92%) patients of 429 randomised were eligible for the analysis. The main reasons for patient ineligibility were wrong stage or incompletely staged disease during central review. The rates of ineligibility and reasons did not differ substantially between the groups. Table 1 shows that patient and tumour characteristics were well balanced across the treatment groups. Of 155 resections, three were wedge resections, 98 were lobectomies, and 54 were pneumonectomies (29 right lung; 25 left lung). In group 2, 155 (80%) of 194 patients began consolidation chemotherapy according to per protocol guidelines.

The amount of chemotherapy delivered per protocol during induction chemotherapy plus radiotherapy did not differ between the groups (group 1, 191 [95%] of 201; group 2, 177 [92%] of 193). 111 (55%) of 202 patients in group 1 and 144 (74%) of 194 in group 2 completed consolidation chemotherapy ( $p<0.0001$ ; figure 1). We administered radiotherapy per protocol or with acceptable variation to 193 (96%) patients in group 1 and to 154 (79%) in group 2 ( $p<0.0001$ ).

Table 2 summarises the toxicities. The most common grade 3 or 4 toxicity was neutropenia in 77 (38%) patients in group 1 and 80 (41%) in group 2. Grade 3 or 4 oesophagitis was reported in 20 (10%) patients in group 1 and 44 (23%) in group 2 ( $p=0.0006$ ). Pneumonitis or other grade 3 or 4 respiratory complications were reported in 18 (9%) patients in group 1 and 28 (14%) in group 2 ( $p=0.116$ ). Grade 3 or 4 nausea or emesis, or both, were reported in 29 (14%)

patients in group 1 and 26 (13%) in group 2 ( $p=0.885$ ). Grade 3 or above overall toxicity during induction chemotherapy plus radiotherapy did not differ between the groups (data not shown), whereas the rate of haematological toxicity was greater in group 2 during consolidation chemotherapy (89 [point estimate 56%] of 159 vs 44 [point estimate 36%] of 121).

No treatment-related deaths were reported during induction treatment in either group. Subsequently, 16 (8%) patients died from causes not attributable to cancer in group 1, including ten within 30 days of thoracotomy. 14 of 16 patients died after pneumonectomy and one after lobectomy, and one patient who did not undergo thoracotomy also died. Causes of death were acute respiratory distress syndrome ( $n=9$ ), other respiratory ( $n=4$ ), cardiac ( $n=2$ ), and haemorrhage ( $n=1$ ). Four (2%) patients in group 2 died from treatment-related causes (non-acute-respiratory-distress-syndrome respiratory [ $n=3$ ] and other [ $n=1$ ]) during or after consolidation chemotherapy plus radiotherapy.

OS was not improved in group 1 versus group 2 (median 23.6 months [IQR 9.0–not reached] vs 22.2 months [9.7–52.7]; hazard ratio (HR) 0.87 [0.70–1.10],  $p=0.24$ ; figure 2B); 145 of 202 patients had died in group 1 versus 155 of 194 in group 2. More patients were alive without progression in group 1 (43 [21%] of 202 vs 22 [11%] of 194;  $p=0.008$ ), but more individuals died without progression in group 1 (36 [18%] of 202 vs 19 [10%] of 194;  $p=0.02$ ) than in group 2. By 5 years, an absolute difference of 7% was noted in favour of the surgical group, with 37 (point estimate 27%) of 202 patients alive versus 24 (point estimate 20%) of 194 (odds ratio 0.63 [0.36–1.10]). No other factor was useful for prediction of 5-year survival with logistic regression.

Several independent predictors of outcome were noted with the Cox OS model, including absence of major weight loss ( $p=0.003$ ), female sex ( $p=0.009$ ), and one N2 nodal station that was positive at diagnosis versus more ( $p=0.024$ ). Treatment group, age, Karnofsky performance status, T stage, lactate dehydrogenase, and histology were not retained in the model. Because different factors determined whether a pneumonectomy or lobectomy was chosen, a survival comparison of the cohorts given these surgeries was not done.

PFS was longer in group 1 than in group 2 (median 12.8 months [IQR 5.3–42.2] vs 10.5 months [4.8–20.6]; HR 0.77 [95% CI 0.62–0.96],  $p=0.017$ ; figure 2A); 159 of 202 patients had progressed or died in group 1 versus 172 of 194 in group 2. At 5 years, 32 (point estimate 22%) of 202 patients in group 1 versus 13 (point estimate 11%) of 194 in group 2 were free of disease.

The postinduction pathological findings in group 1 by T and N category were recorded as proportions of 164 thoracotomies done and of total number ( $n=202$ ) of patients enrolled for each category. The categories were 29 T0N0 (18% thoracotomies and 14% patients); 31 T1N0 (19% and 15%), 16 T2–4N0 (10% and 8%); 85 N1–3 (52%

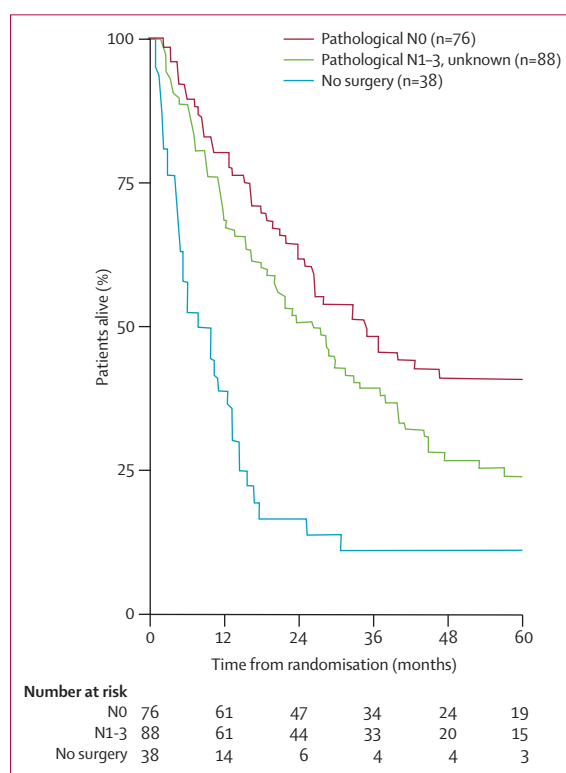
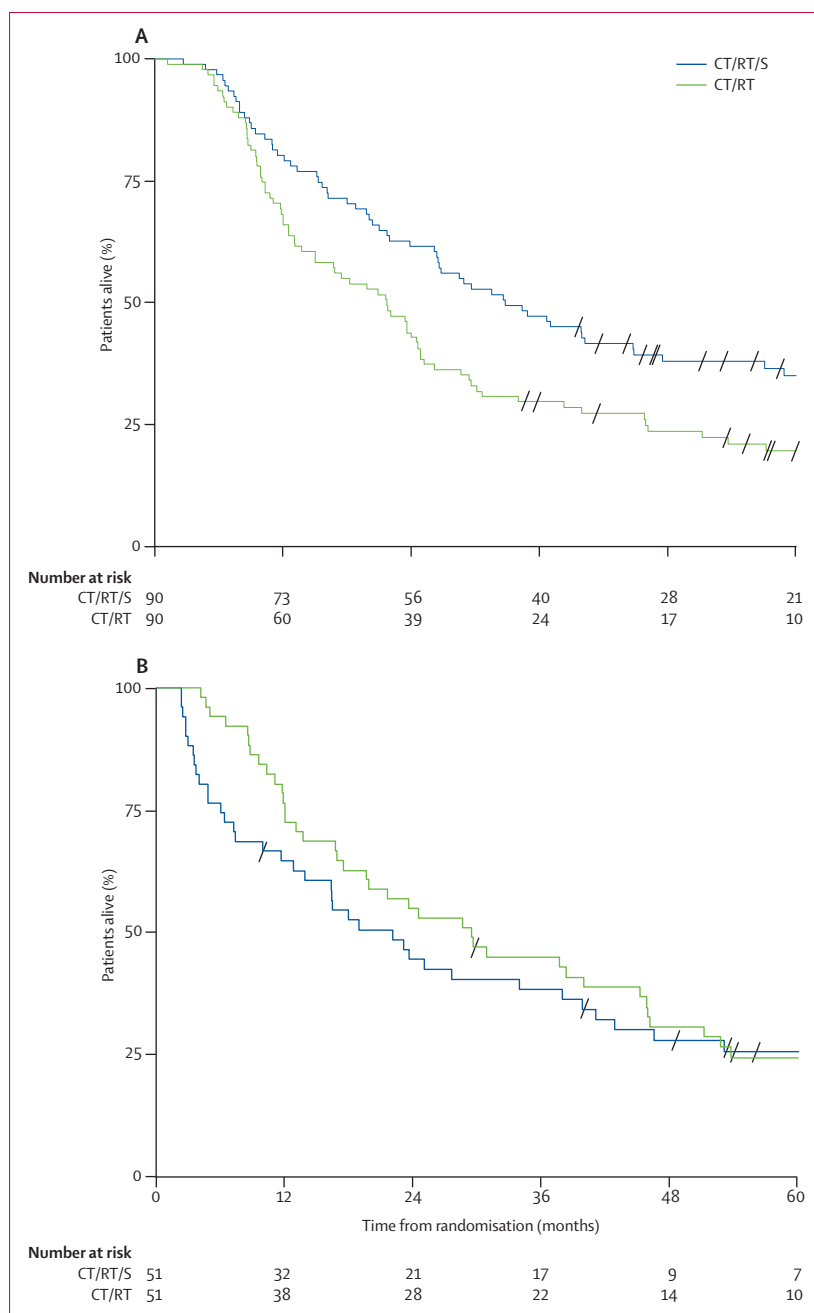


Figure 3: Overall survival in group 1 by pathological nodal substage determined after thoracotomy

and 42%); and 3 unknown (2% and 2%). A pneumonectomy had been done for 13 (45%) of 29 T0N0 specimens. Figure 3 shows OS by postinduction pathological stage according to N status. Median survival time and 5-year survival rates for patients with T (any) N0 were 34.4 months (IQR 15.7–not reached) and 19 (point estimate 41%) of 76, respectively; T(any)N1–3 or unknown, 26.4 months (11.0–57.1) and 15 (point estimate 24%) of 88, respectively; and no surgical resection, 7.9 months (4.2–14.4) and 3 (point estimate 8%) of 38, respectively ( $p<0.0001$  for difference in survival between patients in these three categories; figure 3). Patients in the T0N0 subset had a median survival of 39.8 months (16.4–not reached), and at 5 years six (point estimate 42%) of 29 were alive. Postinduction pathological categories were not known in group 2, thus comparisons between groups were not feasible within TN subsets.

With the exception of fewer local-only relapses in group 1 (21 [10%] of 202) than in group 2 (43 [22%] of 194), no differences were noted in sites of first progression. The sites of these relapses were the primary tumour sites only (5 [2%] of 202 vs 28 [14%] of 194); hilar, mediastinal, or supraclavicular nodes only (14 [7%] of 202 vs 6 [3%] of 194), and both (2 [1%] of 202 vs 9 [5%] of 194). The brain was the only initial site of relapse in 23 (11%) of 202 patients in group 1 versus 29 (15%) of 194 in group 2. Rates of recurrence at other distant sites were 75 (37%) of 202 versus 81 (42%) of 194, respectively.





**Figure 4:** Overall survival of a subset of patients from the intention-to-treat population given lobectomy (A) or pneumonectomy (B) in group 1 versus matched cohorts in group 2

Slash marks represent censored results. CT/RT/S=chemotherapy plus radiotherapy followed by surgery (group 1, n=202). CT/RT=chemotherapy plus radiotherapy (group 2, n=194).

The OS matching analysis for four prestudy factors for group 1 against group 2 subsets was feasible for 90 of 98 lobectomies and 51 of 54 pneumonectomies. Rate of OS was improved in the surgical group if a lobectomy was done compared with the rate in the matched chemotherapy plus radiotherapy group (figure 4A). Median survival time was 33.6 months (IQR 15.6–not

reached) in group 1 versus 21.7 months (10.1–46.0) in group 2 ( $p=0.002$ ); at 5 years, 21 (point estimate 36%) of 90 patients versus ten (point estimate 18%) of 90, respectively, were alive. Rate of OS for patients in group 1 for the pneumonectomy subgroup was non-significantly worse than those for the matched cohort in group 2 (figure 4B). Median survival times were 18.9 months (6.0–46.6) versus 29.4 months (12.0–53.7); at 3 years, 17 (point estimate 36%) of 51 patients versus 22 (point estimate 45%) of 51 were alive; and at 5 years, seven (point estimate 22%) of 51 in group 1 versus ten (point estimate 24%) of 51 in group 2 were alive.

## Discussion

OS was not significantly improved, even though PFS was, in patients who underwent trimodality treatment—ie, concurrent chemotherapy and radiotherapy followed by surgical resection—compared with those given concurrent chemotherapy and radiotherapy without surgery. Rates of 5-year OS were non-significantly improved after trimodality treatment. Reasons for the absence of OS benefit might include inadequate power and reduced delivery of cycles 3 and 4 of chemotherapy in the surgical group. However, whether the additional chemotherapy had any effect in the non-surgical setting is not known.

Another reason for the absence of benefit with surgery might largely relate to the high death rate after pneumonectomy, mainly attributable to acute respiratory distress syndrome and other respiratory causes. On the basis of this finding, we did an exploratory matching analysis that led us to the hypothesis that trimodality treatment could be beneficial if a complete resection with lobectomy can be done after chemotherapy plus radiotherapy, or if mortality from pneumonectomy can be avoided. This type of analysis has limitations because of the possibility of other differences that were not noted when criteria were matched, so it should not be used as the only basis to select treatment. Also, the necessity for pneumonectomy in many patients was probably related to other adverse prognostic factors. 45% of pT0N0 specimens were resected with pneumonectomy, showing that perhaps a large proportion underwent extensive surgery unnecessarily. Thus, this exploratory analysis could be useful in decision making to ensure caution when a trimodality prescription with pneumonectomy is considered.

Both treatment regimens resulted in median and 5-year survival rates that were better than expected on the basis of data from phase II studies in patients with stage IIIA(N2) non-small-cell lung cancer.<sup>11,12</sup> The patients enrolled in our trial with mediastinal nodal (pN2) involvement were judged to be fit for a rigorous treatment regimen and had disease for which chemoradiotherapy alone was deemed the standard therapy, yet was technically resectable. However, this population stands in contrast with other phase III trials in patients with

pN2 disease. The patients who were included in the randomised trials<sup>12,13,22–24</sup> in which induction chemotherapy was followed by surgery versus a surgery-only control group had less extensive N2 disease than those included in our study.

Although the European Organisation for Research and Treatment of Cancer (EORTC) did a phase III trial<sup>25</sup> in which patients with stage IIIA(N2) non-small-cell lung cancer were randomly assigned to surgery or radiotherapy after response to induction chemotherapy, the study differed from ours in several ways. The EORTC control group of chemotherapy followed by radiotherapy is not regarded as standard treatment,<sup>9–11</sup> and the outcome of all the patients is not known because only the responding patients were randomly assigned to treatment unlike in our trial. Similar to our findings, accrual in the EORTC study was protracted, and no OS benefit was noted. The median and 5-year survival rates in both groups of the EORTC study were worse than those in our study, although this difference could be explained partly by the two trials having different entry criteria.

Induction chemotherapy plus radiotherapy were well tolerated by patients in both groups in our study, with excellent treatment compliance. Treatment-related mortality attributable to respiratory causes was worse in the surgical group, and fewer patients could complete consolidation chemotherapy after surgery than in the non-surgery group. However, patients in the concurrent chemotherapy and radiotherapy group had an increased rate of severe oesophagitis and other toxicities during consolidation chemotherapy and radiotherapy, and were less likely to complete the prescribed radiotherapy than were those given surgery.

With the long accrual period needed to complete trials that address whether the inclusion of surgery versus a non-surgical approach is beneficial, a prospective trial is unlikely to be done to validate the hypothesis generated as a result of our exploratory analysis (ie, trimodality approaches are better than bimodality approaches if lobectomies can be done). Thus, medically healthy patients with stage IIIA(N2) non-small-cell lung cancer should be assessed by a team skilled in multimodality treatment, and treatment options can be considered during assessment. On the basis of the findings of our study, patients should be counselled about the risks and potential benefits of definitive chemotherapy plus radiotherapy with and without a surgical resection (preferably by lobectomy).

#### Contributors

KSA, VRR, and ATT were the principal investigators. KSA, VWR, ATT, CS, RHF, and DHJ participated in study design, writing the protocol, review or approval of the final draft of the protocol, patient accrual, study monitoring, and data and toxicity review, discipline review, final data analyses, and interpretation of results. FAS participated in patient accrual, study monitoring, data and toxicity review, discipline review, final data analyses, and interpretation of results. RSS was the study biostatistician, and did all the analyses, participated in the final data analyses, and

interpretation of results. RBL participated in study design, protocol writing or review or approval of the final draft of the protocol, and patient accrual. DRG participated in study design, patient accrual, discipline review, final data analyses, and interpretation of results. YC, WAF, and GD participated in patient accrual. MRG participated in interpretation of results. RCM participated in patient accrual, study monitoring, data and toxicity review, final data analyses, and interpretation of results. JL participated in study monitoring, data and toxicity review, and discipline review. WTS participated in study design. KSA, RSS, VWR, ATT, FAS, CS, YC, RHF, DRG, WAF, GD, DHJ, MRG, RCM, and JDC participated in writing or reviewing the completed report. All authors have approved the report for publication.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

This trial was funded by the National Cancer Institute (PHS Cooperative Agreement grant numbers CA21661, CA37422, CA32115, CA46441, CA77202, CA49957, CA03927, CA25224) with high priority designation, and Canadian Cancer Society (NCIC10362), and administered by the Radiation Therapy Oncology Group (RTOG, R9309), with participation by Southwest Oncology Group, National Cancer Institute of Canada Clinical Trials Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and North Central Cancer Treatment Group. We thank the many North American Intergroup discipline chairs and others who provided advice or assistance during the design of this study or while the study was in progress; the members of the Lung Cancer Committees of the Southwest Oncology Group, National Cancer Institute of Canada Clinical Trials Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and the North Central Cancer Treatment Group for their support of this study over the long accrual period; and especially the lung cancer survivors who were treated and followed up on this protocol, and the lay advocates who supported this trial design.

#### References

- Mountain CF. Prognostic implications of the International Staging System for lung cancer. *Semin Oncol* 1988; 3: 236–45.
- Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Amer* 1987; 67: 1037–49.
- Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59: 1874–81.
- Johnson DH, Einhorn LH, Bartolucci A, et al. Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. *Annals Int Med* 1990; 113: 33–38.
- Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell-lung cancer. *N Engl J Med* 1990; 323: 940–45.
- Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995; 87: 198–205.
- LeChevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in non-resectable non-small cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991; 83: 417–23.
- Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer—a meta-analysis. *Ann Intern Med* 1996; 125: 723–29.
- Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; 17: 2692–69.
- Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential versus concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer: RTOG 9410. *Proc Am Soc Clin Oncol* 2003; 22: 621 (abstr).

- 11 Farray D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small-cell lung cancer. *J Clin Oncol* 2005; **23**: 3257–69.
- 12 Eberhardt WE, Albain KS, Pass H, et al. Induction treatment before surgery for non-small cell lung cancer: IASLC consensus report. *Lung Cancer* 2003; **42**: S9–14.
- 13 Pisters K, Mirkovic N, Pass H, Albain KS. Preoperative chemotherapy/radiation therapy for early stage and locally advanced non-small cell lung carcinoma. In: Pass HI, Carbone DP, Johnson DH, et al, eds. *Lung cancer: principles and practice*, 3rd edn. Philadelphia: JB Lippincott Williams and Wilkins, 2005: 626–49.
- 14 Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA(N2) and IIIB non-small cell lung cancer: Mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995; **13**: 1880–92.
- 15 Albain KS, Crowley JJ, Turrisi AT, et al. Concurrent cisplatin, etoposide and chest radiotherapy in pathological stage IIIB non-small cell lung cancer: a Southwest Oncology Group Study (SWOG-9019). *J Clin Oncol* 2002; **20**: 3454–60.
- 16 Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis* 1974; **27**: 365–75.
- 17 Lakatos E. Sample size based on the long-rank statistic in complex clinical trials. *Biometrics* 1988; **44**: 229–41.
- 18 Cox D. Regression models and life-tables (with discussion). *J R Stat Soc, Series B* 1972; **34**: 187–220.
- 19 Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
- 20 Albain KS, Scott CB, Rusch VR, et al. Phase III comparison of concurrent chemotherapy plus radiotherapy (CT/RT) and CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer: initial results from intergroup trial 0139 (RTOG 93-09). *Proc Am Soc Clin Oncol* 2003; **22**: 621 (abstr).
- 21 Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer: Outcomes update of North American Intergroup 0139 (RTOG-9309). *J Clin Oncol* 2005; **23**: 624s (abstr).
- 22 Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing preoperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer. *J Natl Cancer Inst* 1994; **86**: 673–30.
- 23 Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994; **330**: 153–58.
- 24 Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002; **20**: 247–53.
- 25 van Meerbeeck JP, Kramer GWPM, Van Schil PEY, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007; **99**: 442–50.