Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone

On behalf of the European Organisation for Research and Treatment of Cancer-Lung Cancer Group

Background Induction chemotherapy before surgical resection increases survival compared with surgical resection alone in patients with stage IIIA-N2 non–small-cell lung cancer (NSCLC). We hypothesized that, following a response to induction chemotherapy, surgical resection would be superior to thoracic radiotherapy as locoregional therapy.

Methods Selected patients with histologic or cytologic proven stage IIIA-N2 NSCLC were given three cycles of platinum-based induction chemotherapy. Responding patients were subsequently randomly assigned to surgical resection or radiotherapy. Survival curves were estimated using Kaplan–Meier analyses from time of randomization.

Results Induction chemotherapy resulted in a response rate of 61% (95% confidence interval [CI] = 57% to 65%) among the 579 eligible patients. A total of 167 patients were allocated to resection and 165 to radiotherapy. Of the 154 (92%) patients who underwent surgery, 14% had an exploratory thoracotomy, 50% a radical resection, 42% a pathologic downstaging, and 5% a pathologic complete response; 4% died after surgery. Postoperative radiotherapy was administered to 62 (40%) of patients in the surgery arm. Among the 154 (93%) irradiated patients, overall compliance to the radiotherapy prescription was 55%, and grade 3/4 acute and late esophageal and pulmonary toxic effects occurred in 4% and 7%; one patient died of radiation pneumonitis. Median and 5-year overall survival for patients randomly assigned to resection versus radiotherapy were 16.4 versus 17.5 months and 15.7% versus 14%, respectively (hazard ratio = 1.06, 95% CI = 0.84 to 1.35). Rates of progression-free survival were also similar in both groups.

Conclusion In selected patients with pathologically proven stage IIIA-N2 NSCLC and a response to induction chemotherapy, surgical resection did not improve overall or progression-free survival compared with radiotherapy. In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment for these patients.

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An estimated 1.2 million new cases of lung cancer occur yearly worldwide, resulting in annual fatalities of 183 000 in Europe and 160 000 in the United States (1). Eighty percent of all lung cancers are non–small-cell lung cancer (NSCLC), and approximately 15% of patients with NSCLC are diagnosed with stage IIIA-N2 disease (2). This subgroup is heterogeneous, with lymph nodes that are only microscopically invaded to those that are radiologically visible with bulky ipsilateral mediastinal lymph node involvement (3). Surgical resection in selected patients results in 5-year survival rates of 7%–24% (4). Preoperative chemotherapy has been shown to increase 5-year survival to 17%–36% (5–7). The combination of platinum-based chemotherapy and thoracic

Affiliations of authors: Department of Respiratory Medicine, University Hospital Ghent, Gent, Belgium (JPVM); Department of Radiation Therapy, Arnhem Radiotherapeutic Institute, Arnhem, The Netherlands (GWPMK); Departments of Respiratory Medicine and Thoracic Surgery, University Hospital Antwerp, Antwerp, Belgium (JPVM, PEYVS); European Organisation for Research and Treatment of Cancer Data Center, Brussels, Belgium (CL, CD); Departments of Pulmonology and Medical Oncology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands (EFS, GG); Department of Pulmonology, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands (FS); Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands (VCTH); Department of Pulmonology, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, The Netherlands (BB); Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands (NVZ); Departments of Pulmonology and Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands (JPVM, TAWS).

Correspondence to: Jan P. van Meerbeeck, MD, PhD, Department of Respiratory Medicine, 7K12IE, University Hospital Ghent, De Pintelaan 185, 9000 Gent, Belgium (e-mail: jan.vanmeerbeeck@ugent.be).

Gijs W. P. M. Kramer is deceased.

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radiotherapy yielded a 5-year survival rate of 15% in a meta-analysis (8), and this combination has since been considered standard treatment for patients with unresectable stage IIIA disease. In a prospective study (9), concurrent chemoradiotherapy resulted in a 5-year survival rate of 20%.

Based on the results of these previous studies, we hypothesized that surgery may be superior to radiotherapy following induction chemotherapy. Therefore, we performed a large multicenter prospective randomized trial to compare surgery with radiotherapy in patients with stage IIIA-N2 NSCLC who showed a response to induction chemotherapy.

Patients and Methods

Eligible patients had to have cytologic or histologic proof of unresectable stage IIIA-N2 NSCLC (2). Staging included physical examination, a computed tomography (CT) scan of the thorax, and ultrasound or CT scan of the upper abdomen. Guidelines for unresectability were as follows: 1) any N2 involvement by a non-squamous carcinoma; 2) in case of squamous cell carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumor and level 5 and 6 for a left-sided tumor. N2 found only at thoracotomy after a negative staging mediastinoscopy was not necessarily considered to be unresectable. Tumors and/or any involved mediastinal lymph node(s) had to be unidimensionally measurable on CT scan. Patients had to be older than 18 years, have a World Health Organization (WHO) performance status of 0–2, show no evidence of pulmonary fibrosis, and be considered fit for the combined modality treatment by their local multidisciplinary team. Patients with preexisting neurotoxicity, with infections, who had had prior therapy for NSCLC, or had concurrent or prior malignancy were excluded. Patients had to give written informed consent for participation.

Induction chemotherapy consisted of three cycles of cisplatin, at a dose of at least 80 mg/m^2 per cycle, or carboplatin, at a target area under the curve of at least 5 per cycle, combined with at least one other chemotherapy drug. Three phase 2 trials investigating the activity of novel drug combinations (10–12) were nested within this study.

Response was evaluated with CT scan after at least two cycles of induction chemotherapy and scored according to WHO criteria (13), but confirmation was not required. Eligibility was reassessed before random assignment. Only patients showing a response (complete, partial, or minor) to induction chemotherapy were eligible for random assignment to either surgery or radiotherapy after stratification for type of response, histologic subtype, and institution (14). Locoregional therapy (i.e., surgery or radiotherapy) had to start within 6 weeks of random assignment. The standards, definitions, and criteria of radiotherapy and surgery have been reported previously (15,16). A compliance score was defined based on the following radiotherapy prescription requirements: 1) an interval from the last day of induction chemotherapy until the start of radiotherapy of less than 10 weeks, 2) the use of three-dimensional planning, 3) the use of lung tissue correction, 4) a dosage administered to the primary tumor and involved mediastinum of 60–62.5 Gy and to the uninvolved mediastinum of 40–46 Gy, 5) a fractionation size of 1.95–2.05 Gy, 6) a number of fractions of 30–32, and 7) a total treatment duration of 40–46 days (17). Mediastinal downstaging was defined as the absence of tumor on pathologic examination of the resected mediastinal lymph nodes. A resection was considered to be complete if, following review of the surgery and pathology report by one of the authors (P. E. Y. V. Schil), both surgical margins and the highest mediastinal lymph node were found to be free of tumor. Postoperative radiotherapy consisting of 56 Gy in once-daily fractions of 2 Gy was recommended in cases of incomplete resection and had to start between the 4th and 10th postoperative week.

Pulmonary function was measured at least once before and after surgery or radiotherapy. The management of treatment-related toxic effects and complications was left to the local investigator. Surgical complications were recorded descriptively. Radiotherapy toxicity was scored according to the National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria (18). Patients underwent follow-up visits every 3 months for 2 years and every 6 months thereafter, which included clinical evaluation, a chest-x-ray, and additional investigations when clinically indicated.

Statistical Analysis and Trial Conduct

The primary endpoint of the trial was overall survival measured from the day of random assignment and analyzed on all randomly assigned patients according to the intention-to-treat principle. Secondary endpoints were progression-free survival and safety. Progression-free survival was defined as time to progression or death, whichever came first, and both progression and death were considered as events. Assuming a 15% 5-year survival with radiotherapy, a two-sided type 1 error of 5%, and a power of 80%, 292 events were necessary to detect an increase to 25% in the 5-year survival with surgery. Assuming 8 years of accrual and 2 further years of follow-up, 358 patients had to be randomly assigned. At an

CONTEXT AND CAVEATS

Prior knowledge

Compared with surgery alone, induction chemotherapy before surgery improves survival of patients with stage IIIA NSCLC.

Study design

A randomized controlled trial of surgery versus thoracic radiotherapy in patients with stage IIIA-N2 NSCLC who responded to induction chemotherapy.

Contributions

Median survival time and 5-year overall survival rates for patients who underwent surgery were 16.4 months and 15.7%; those for patients who underwent radiotherapy were 17.5 months and 14%.

Implications

In patients with stage IIIA-N2 NSCLC who respond to induction chemotherapy, subsequent surgery did not improve overall or progression-free survival compared with radiation therapy. Radiotherapy may be the preferred treatment for these patients, given its low morbidity and mortality.

Limitations

Patient selection may have been affected by changing standards for tumor staging during trial accrual. Outcome may have been affected by changing treatment standards during the trial.

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historically assumed 1:1 randomization rate of 56%, 640 patients had to be accrued. The trial was closed after randomization of slightly fewer patients (332) than initially foreseen, after statistician's advice that this early closure would not interfere with its power because the observed number of deaths for the primary endpoint (279) was close to that required at the time of the analysis. The posterior power as computed with EAST v4.1, (Cytel Software Corporation, Cambridge, MA) was approximately 75%. Randomization was performed by a central computer–generated random allocation sequence at the European Organisation for Research and Treatment of Cancer (EORTC) Data Center. Both arms were compared using a two-sided log-rank test, and survival curves were estimated using the Kaplan–Meier technique. The statistical significance level was set at 0.05, and all comparisons were two-sided. Uni- and multivariable analyses of prognostic factors using the Cox proportional hazards model were conducted on all randomly assigned patients and per treatment arm. Proportionality was checked visually based on the Kaplan–Meier survival curves. Because there was no suggestion of nonproportional hazards, a formal test was not applied.

Two interim analyses on all outcomes of the study were conducted after 80 and 146 deaths. Stopping rules for efficacy were specified a priori in the protocol, considering an alpha-spending function with O'Brien and Fleming boundary. The results of these interim analyses were declared to the members of the Independent Data Monitoring Committee only, who recommended continuing the trial. Following an audit of radiotherapy quality control and according to recommendations given during the first Independent Data Monitoring Committee review, the protocol was amended in 1999 as follows: 1) Radiotherapy prescription needed to be better detailed and adhered to (14,17). 2) Only the following induction chemotherapy regimens were allowed: cisplatin–docetaxel, cisplatin–gemcitabine, carboplatin–paclitaxel, cisplatin–vindesin (with or without ifosfamide), carboplatin–etoposide, and cisplatin–ifosfamide–mitomycin. 3) Uniform definitions of unresectability and complete resection were introduced and the available data reviewed accordingly. 4) A formal process of reporting serious adverse events and late treatment–related side effects was implemented. The study protocol and all amendments were approved by the Protocol Review Committee of the EORTC and the ethical committees of all participating institutions. This study was registered at www.clinicaltrials.gov with number NCT00002623.

Results

A total of 582 patients were registered from December 1, 1994, to December 1, 2002, from 41 institutions of the EORTC-Lung Cancer Group (EORTC-LCG). The study was prematurely closed due to lower than planned accrual at a slightly lower (n = 332) than the required number of randomly assigned patients. This study was analyzed in December 2005 after a median follow-up of approximately 6 years, and no losses to follow-up for overall survival occurred in the randomly assigned patients. The CONSORT diagram is shown in Fig. 1. Patient, tumor, and induction chemotherapy characteristics of the 579 eligible and the 332 randomly assigned patients are provided in Table 1.

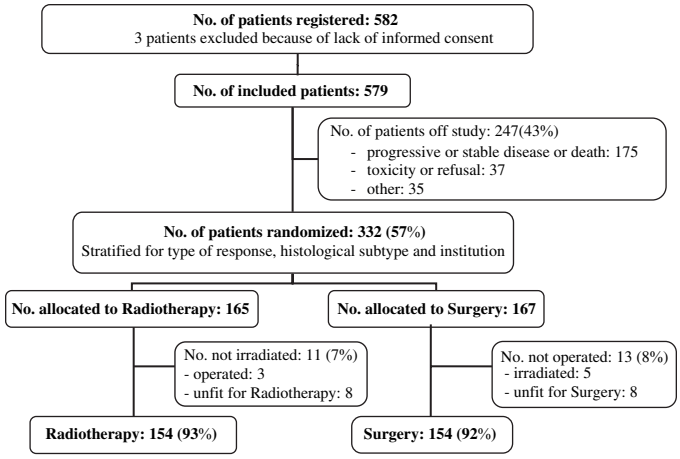

Fig. 1. Trial design and CONSORT diagram. This flow chart describes the different populations included in the study analysis: registered (n = 582), eligible (n = 579), and randomly assigned (n = 332). Patients were allocated and actually treated as per protocol with either surgery or radiotherapy.

Induction chemotherapy consisted mainly of a platinum/gemcitabine (40%) or a platinum/taxane combination (21%) (19). Eighty-seven percent of patients received three cycles of induction chemotherapy; nine patients never started induction chemotherapy. An overall response rate of 61% (95% confidence interval [CI] = 57% to 65%) was observed. Thirty-eight responding patients were not randomly assigned because of refusal (n = 14), inoperability (n = 15), unresectability (n = 5), toxicity of induction chemotherapy (n = 2), or for unknown causes (n = 2). Retrospective analysis by response type in the 332 randomly assigned patients showed that 316 had an objective response, 12 had stable disease, and 4 progressed on induction chemotherapy. Of the 16 nonresponding patients above, 6 were allocated to surgery and 10 to radiotherapy. The patient and tumor characteristics of the randomly assigned patients and the distribution of the observed responses to induction chemotherapy were well balanced.

One hundred fifty-four (93%) of the 165 patients in the radiotherapy arm were irradiated (Table 2). The results of the radiotherapy quality assurance have been published (17). The overall compliance to the radiotherapy prescribed was 55%. The median overall treatment time from start of induction chemotherapy to the end of radiotherapy was 145 days (range = 91–194). Acute grade 3/4 esophageal and pulmonary toxic effects were observed in one patient (<1%) and five patients (4%), respectively. Late pulmonary and esophageal fibrosis occurred in 11 (7%) patients and 1 (<1%) patient, respectively, and one patient died of radiation pneumonitis.

One hundred fifty-four (92%) of the 167 patients in the surgery arm underwent surgery (Table 3). The results of the operated patients have been reported previously (15). Briefly, 14% had an exploratory thoracotomy, 50% a radical resection, 42% a pathologic downstaging, and 5% a pathologic complete response; 4% died within 30 days following surgery. Resection was performed after a median of 49 days (range = 22–86) after the last cycle of induction chemotherapy. Postoperative radiotherapy was administered to 62 (40%) patients, among whom two cases of grade

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Table 1. Characteristics of patients, tumors, and induction chemotherapy*

Population variable	All registered patients (N = 579)	Randomly assigned patients	
		Radiotherapy arm (n = 165)	Surgery arm (n = 167)
Sex, n (%)			
Male	427 (74)	127 (77)	119 (71)
Female	152 (26)	38 (23)	48 (29)
Age, median (range), y†	61 (29–78)	62 (33–76)	61 (29–78)
Caucasian ethnicity, n (%)	552 (95)	160 (97)	162 (97)
Histologic subtype, n (%)			
Squamous carcinoma	NA	66 (40)	65 (39)
Adenocarcinoma	NA	46 (28)	57 (34)
Large cell carcinoma	NA	46 (28)	41 (25)
Other		7 (4)	4 (2)
Proof of N2 by, n (%)			
Histology	528 (91)	152 (92)	155 (93)
Cytology	41 (7)	8 (5)	11 (7)
Clinically only	10 (2)	5 (3)	1 (1)
Type of biopsy, n (%)			
Mediastinoscopy	478 (83)	135 (82)	141 (84)
VATS	6 (1)	1 (1)	4 (2)
Thoracotomy	34 (6)	13 (8)	8 (5)
Needle procedure‡	56 (10)	13 (8)	14 (8)
cT at registration, n (%)			
cT1	67 (12)	21 (13)	20 (12)
cT2	396 (68)	119 (72)	120 (73)
cT3	100 (17)	25 (15)	25 (16)
cT4	13 (2)	0	1
other/unspecified	3 (1)	1	0
Patients receiving three cycles of induction chemotherapy, n (%)	503 (87)	165 (100)	166 (99)
Median interval between registration and random assignment, days (range)	NA	71 (0–113)	73 (0–117)
Response on induction chemotherapy, n (%)			
Complete response	22 (4)	8 (5)	12 (7)
Partial and minor response	332 (57)	147 (89)	149 (89)
Stable disease	105 (18)	8 (5)	4 (2)
Disease progression	80 (14)	2 (1)	2 (1)

* This table describes the characteristics of the patients, their tumors, and their response to the induction chemotherapy in the entire group of eligible patients and in both randomly assigned subgroups, regardless whether they actually received the allocated treatment. All percentages are rounded. VATS = video-assisted thoracic surgery; cT = clinical tumor stage; NA = not available.

† At registration.

‡ Including transbronchial and transthoracic fine-needle aspiration or core biopsy.

3 acute esophagitis and one case of grade 4 acute pneumonitis were observed.

Median overall survival, estimated from the time of registration in all 579 eligible patients, was 15.4 months (95% CI = 142 to 17.3). The results of overall and progression-free survival, estimated from the day of randomization, were similar in the 332 patients allocated to both treatment arms (Table 4). Median survival time and 5-year overall survival percentages were 17.5 months and 14% in the radiotherapy arm and 16.4 months and 15.7% in the surgery arm, respectively. Kaplan–Meier analyses showed that overall survival (Fig. 2) and progression-free survival (Fig. 3) were similar among patients in both arms. Site of first relapse was more often locoregional in the radiotherapy arm and more often distant in the surgery arm (Table 4).

Of all the baseline characteristics and stratification factors of the randomly assigned patients that were included in the multivariable analyses, only histologic subtype was prognostic, with a higher risk of death for patients with nonsquamous histologies. After adjusting for histologic subtype, the treatment comparison was still not statistically significant. In the radiotherapy arm, none of the patient or treatment characteristics—including randomization before or after the protocol amendment—was prognostic. In the surgery arm, extent and type of resection were prognostic factors (for lobectomy versus pneumonectomy, hazard ratio [HR] = 0.59, 95% CI = 0.40 to 0.87, and for complete resection versus incomplete resection, HR = 0.46, 95% CI = 0.32 to 0.67). Unplanned exploratory subgroup analyses were performed in the 154 surgery-arm patients (Table 5). Patients who underwent a (bi-)lobectomy, had a complete resection, had pathologically proven mediastinal clearance, had a statistically significantly better outcome than patients who underwent a pneumonectomy, had an incomplete resection, or had no mediastinal clearance. Patients who received postoperative radiotherapy had similar overall survival outcomes as patients who did not. Multivariable analysis of survival showed that extent and completeness of resection, mediastinal clearance, and postoperative radiotherapy were all statistically significant

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Table 2. Characteristics of locoregional treatment in the thoracic radiotherapy arm (N = 154)*

Protocol prescription	No. of patients treated according to prescription (%)
No. of fractions given = 30–32	131 (85)
Fraction size = 1.95–2.05 Gy	134 (87)
Duration = 40–46 days	123 (80)
Interval between	
Day 1 of last cycle of induction chemotherapy and day 1 of radiotherapy within 10 wk	133 (86)
Day 1 of last cycle of induction chemotherapy and random assignment within 4 wk	93 (60)
Random assignment and day 1 of radiotherapy within 6 wk	136 (82)
Planning CT scan	
Performed	141 (92)
With lung correction	138 (90)
Dose and location of radiation	
Primary tumor (60–62.5 Gy)	129 (84)
Mediastinum	
Involved (60–62.5 Gy)	115 (75)
Uninvolved (40–46 Gy)	134 (87)

* These figures relate to all patients who were allocated to the radiotherapy arm and were actually irradiated. CT = computed tomography.

factors. However, due to the small number of patients in these subgroups, these results should be considered with caution.

Discussion

This large randomized multicenter study demonstrated that surgery did not improve survival after a radiologic response to induction chemotherapy in patients with unresectable stage IIIA-N2 NSCLC as compared with radiotherapy. These results are important because several centers routinely use induction chemotherapy followed by surgery to treat patients with this stage of disease based on small randomized studies that showed that surgery alone is inferior to perioperative chemotherapy and surgery in stage IIIA patients (5–7). The results of this study are robust in terms of numbers and mature in terms of follow-up and are similar to those observed in trials with a similar hypothesis but with a different design (20,21) The North American Intergroup Trialists recently reported a median survival rate of 23.6 and 22.2 months for induction chemoradiotherapy with or without resection, respectively.

The best treatment option for patients with stage IIIA-N2 has been debated. Part of the debate is caused by the heterogeneity of presentation at diagnosis, varying from intracapsular involvement of a single lymph node, in which surgery is indicated, to bulky mediastinal invasion, in which radiotherapy has been standard treatment until approximately a decade ago. A strength of our study is its requirement of pathologic proof of mediastinal involvement and the random assignment of responders only. Although the definition of nonresectable tumor was left to the judgment of the local surgeon, clear guidelines were provided, and surgery and pathology reports were reviewed centrally.

The limitations of this study rely mainly on evolving staging and treatment standards in the course of its accrual. We strongly feel that these do not influence the conclusions. One possible limitation is stage migration; this will affect patient selection but is equally distributed over both arms by the process of randomization. Another is that changes in treatment standards occurred in both arms. However, their net magnitude on the outcome is likely to be limited, as illustrated by the lack of difference in survival among the radiotherapy patients who were randomly assigned before and after the protocol amendment.

The complete resection rate in this series can be considered low in comparison with others (20,21), but it should be interpreted with the definition that became the later standard (22). The feasibility of a sequential trimodality approach in patients with N2 disease, which was proven by mediastinoscopy, was explored in Cancer and Leukemia Group B (CALGB) trial 8935 (23). In that trial, 74 patients were initially treated by two cycles of induction chemotherapy consisting of cisplatin and vinblastine. In patients with response or stable disease, surgical resection was performed followed by sequential adjuvant chemoradiotherapy. Sixty-three patients in CALGB 8935 underwent an exploratory thoracotomy with 46 (75%) having resectable lesions. Applying the same criteria for complete resection as in our study, 23 patients or 36.5% of those undergoing thoracotomy had a complete resection. In only 10 patients, was the disease pathologically downstaged, and there were no pathologic complete responses. Operative mortality was

Table 3. Characteristics of locoregional treatment in the surgical resection arm (N = 154)*

Characteristic	No. of patients with this characteristic (%)
Extent of resection	
Pneumonectomy	72 (47)
Right-sided	38 (25)
Left-sided	33 (22)
(Bi-)lobectomy	59 (38)
Exploratory thoracotomy	22 (14)
Other (remediastinoscopy)	1 (<1)
Type of resection	
Complete	77 (50)
Pathologically complete	8 (5)
Downstaging	
ypN0	39 (25)
ypN1	25 (16)
ypN2	86 (56)
ypN3	1 (1)
missing	3 (2)
Operative mortality within 30 days	
Overall	6 (4)
After pneumonectomy	5 (7)
After right-sided pneumonectomy	2 (5)
After left-sided pneumonectomy	3 (9)
After lobectomy	0 (0)
After exploratory thoracotomy	1 (5)
Postoperative radiotherapy	62 (40)
Dosage (Gy), median (range)	50 (0–60)
No. of fractions, median (range)	25 (8–30)

* These figures relate to all patients who were allocated to the surgery arm and were actually operated on. Mortality rates are expressed as number of deceased within 30 days/number with the specific type of resection. ypN = pathologic lymph node stage after induction therapy.

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Table 4. Outcome after random assignment*

Outcome	Radiotherapy arm (N = 165)	Surgery arm (N = 167)	P†
Median follow-up, mo	73	67	
No. deceased (%)	141 (86)	138 (83)	
Overall survival (95% CI)			
Median, mo	17.5 (15.8 to 23.2)	16.4 (13.3 to 19.0)	
2 y, %	41 (33 to 47.9)	35 (28 to 42)	
5 y, %	14 (9 to 20)	15.7 (10 to 22)	
Hazard ratio (95% CI)	1 (referent)	1.06 (0.84 to 1.35)	.6
No. progressing (%)	130 (79)	115 (69)	
Site of first relapse			
Locoregional	71 (55)‡	37 (32)‡	
Distant	50 (39)‡	70 (61)‡	
Both	9 (7)‡	8 (7)‡	
Progression-free survival (95% CI)			
Median, mo	11.3 (8.9 to 12.7)	9 (7.6 to 11.2)	
2 y, %	24 (18 to 31)	27 (20 to 33)	
Hazard ratio (95% CI)	1 (referent)	1.06 (0.85 to 1.33)	.6

* These figures relate to all randomly assigned patients on intention-to-treat basis. CI = confidence interval.

† *P* values were calculated using a two-sided log-rank test.

‡ Percentage of the patients progressing in either arm.

3.2%, and 7-year overall survival was 10% (24). Thus, in CALGB 8935, the complete resection rate was less than 40% after two cycles of induction chemotherapy, with only a small fraction of patients having a pathologic downstaging. In this study, applying the same criteria, three cycles of induction chemotherapy yielded a higher resectability rate.

The survival of the not–completely resected patients in this study is worse than that of patients in the radiotherapy arm. This difference may be explained by the fact that there is within the radiotherapy arm, a subgroup of patients with pathologically complete response and a subgroup of patients with mediastinal downstaging. Several series have shown that pathologic complete resection and mediastinal downstaging are stronger predictive

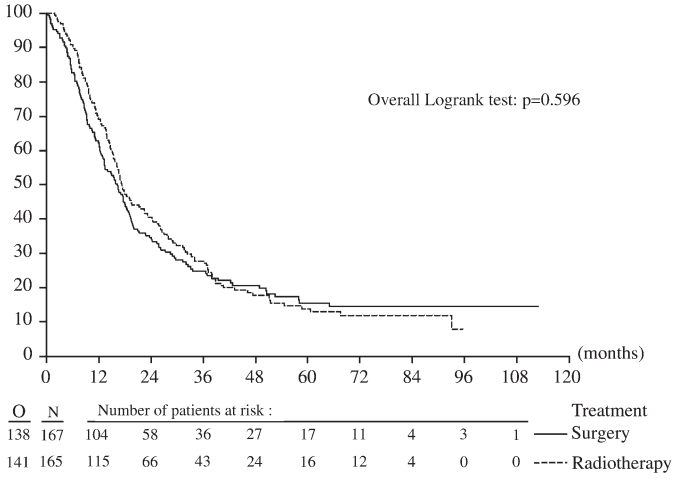

Fig. 2. Overall survival rates estimated from time of randomization using Kaplan–Meier analyses. *P* value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.84 to 1.35; *P* = .596.

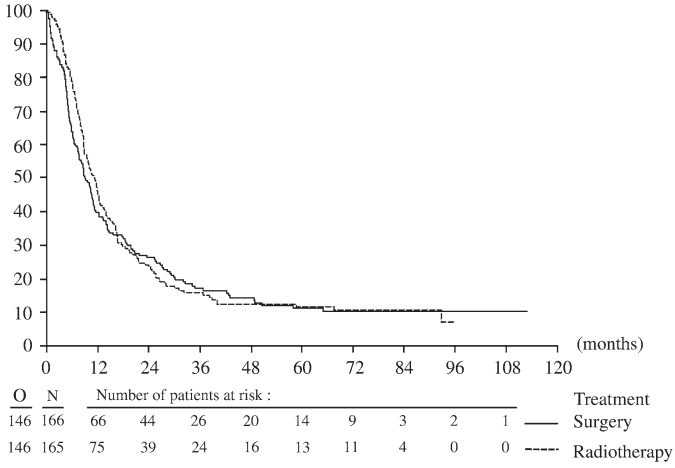

Fig. 3. Progression-free survival rates estimated from time of randomization using Kaplan–Meier analyses. *P* value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.85 to 1.33; *P* = .605.

factors than complete resection (25,26). The number of patients in these two subgroups was not determined but is estimated to be similar to that of the corresponding subgroups in the surgery arm by the process of randomization after induction therapy.

The observed high rate of pneumonectomies in this trial was likely the result of the prevailing opinion among the surgical community during its initial years—i.e., in patients with N2 disease, the whole lung had to be removed. Later, lobectomy with systematic nodal dissection was regarded by most surgeons to be adequate treatment, provided that a complete resection was performed (15,27). In subgroup analysis, we observed a statistically significantly better outcome after (bi-)lobectomy than after pneumonectomy, and this difference has also been observed in the North American Intergroup Trial (21). Pneumonectomy as such is also a known independent negative prognostic factor (28,29), due in part to the higher stage of the disease in patients who require this extensive operation and also to an increased operative mortality associated with this procedure, especially for right-sided tumors. Surgical expertise and hospital volume are determinants of outcome and complication rate of lung cancer surgery (30). However, we observed a low postoperative mortality rate in our study, even among patients who underwent right-sided pneumonectomy. Patient selection may have contributed to this observation (247 patients were excluded for surgery or radiation therapy due to inadequate response). Furthermore, postoperative mortality is markedly high after chemoradiation (21), suggesting a possible detrimental effect of this induction combination.

Surgery is highly unlikely to be beneficial when persistent mediastinal involvement is present after induction treatment, as shown in this study and by others (25,26). Whether these patients should be offered further radical radiotherapy is debatable because their disease will relapse mainly as distant metastases. Hence, the assessment of mediastinal clearance becomes very important. Fluoro-desoxy-glucose positron emission tomography scan, endoscopic ultrasound, and remediastinoscopy all claim a higher accuracy than CTscan in restaging after induction therapy, and the techniques may complement each other (31). Whether only

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Table 5. Exploratory analyses in 154 patients in the resection surgery arm*

Subgroup	N	Median OS, months (95% CI)	5-year OS, %	*P*, Univariate analysis	*P*, Multivariable analysis
Extent of resection				.009	.03
(Bi-)lobectomy	58	25.4 (17.7 to 48.9)	27		
Pneumonectomy	72	13.4 (11.1 to 19.5)	12		
Mediastinal status				<.001	.04
ypN0–1	64	22.7 (17.6 to 42.7)	29		
ypN2	86	14.9 (11.2 to 18.5)	7		
Type of resection				<.001	.01
Complete	77	24.1 (16.7 to 42.4)	27		
Incomplete	76	12.1 (9.5 to 17.1)	7		
No PORT	92	14.1 (11.2 to 19.9)	19	.6	.004
PORT	62	18.0 (15.0 to 25.9)	13		

* OS = overall survival; PORT = postoperative radiotherapy; CI = confidence interval; ypN = pathologic N after induction therapy. *P* values were calculated using a two-sided log-rank test.

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patients with mediastinal clearance should be offered surgery remains uncertain. Only an adequately powered trial, in which patients with proven mediastinal clearance are randomly assigned between surgery and radiotherapy, can truly address this question (32). The EORTC-LCG is considering such a study.

The induction treatment used in this study was platinum-based chemotherapy. Although several different regimens were used, nearly all randomly assigned patients received three cycles, and major responses were achieved in more than 50% of them, similar to the results obtained in other series of induction chemotherapy (33,34). The rate of pathologic complete remission is lower with induction chemotherapy alone when compared with chemoradiotherapy (9,35). Although pathologically complete response has predictive importance in other tumor types, it is still unknown whether response has relevance for long-term survival in NSCLC. Furthermore, although chemoradiation per se does not increase the pneumonectomy rate, it is associated with higher rates of adult respiratory distress syndrome, bronchopleural fistula, and empyema (15). In a multicenter trial among IIIA-N2 NSCLC patients in Germany (36), the addition of twice-daily chemoradiation to induction chemotherapy, followed by resection, had no impact on outcome compared with induction chemotherapy and resection only but contributed to a statistically significantly higher rate of grade 3/4 esophagitis. In the US Intergroup Trial (21), the rate of severe postoperative complications and operative mortality was higher than that in our study. A Swiss cooperative group study (26) reported a pathologic remission rate of 19% using cisplatin and docetaxel induction chemotherapy and observed a low operative morbidity and mortality and high survival rates, suggesting that third-generation induction chemotherapy might be superior to second-generation concurrent chemoradiotherapy. However, we could not reproduce the high response rate of this combination in a multicenter-nested phase 2 trial performed within our trial (12). It is to be expected that improvements in radiotherapy timing, planning, and fractionation, together with the use of better tolerated chemotherapy agents or targeted agents, will result in better compliance and reduce the complication rate of concurrent chemoradiation (37). The role of the intensity of the induction treatment is the subject of an ongoing randomized US trial (38).

During the 8 years that this trial was ongoing, radiotherapy standards underwent substantial improvements. This change in practice was addressed by a formal protocol-specified amendment to the prescription requirements. The tumor volume irradiated encompassed the prechemotherapy tumor areas with a margin that can be considered as optimal. Geographic misses have been reported to occur in reconstructing prechemotherapy target volumes in 26% of patients (39). This can result in a lower locoregional control, but few data from randomized trials on treating pre- or postchemotherapy target volumes exist (40). Of more concern may be the interval between induction chemotherapy and the start of radiotherapy. Although 86% of patients in the radiotherapy arm started their radiotherapy within the prescribed 70 days of their last induction chemotherapy cycle, it has been shown that 41% of tumors progress when a mean interval of 80 days between induction chemotherapy and radiotherapy is present (41). Although only five patients were not treated after randomization because of clinical deterioration or tumor progression, this delay could be responsible for the high observed local relapse rate in the radiotherapy arm. Similar considerations apply with regard to the overall treatment time. The use of concurrent chemoradiotherapy has been reported to result in lower overall treatment times and is associated with better short-term survival results at the risk of higher toxicity (42). Our observed median overall treatment time of 145 days in the radiotherapy arm could be alone responsible for the observed difference in survival with the concurrent chemoradiotherapy arm of the Intergroup Trial (21), but other explanations are possible. Survival in the Intergroup Trial was counted from time of randomization, and thus, a median of 2.5 months has to be added to compare survival times in this trial with those of studies with upfront randomization (20,21,36). Furthermore, most studies also combined induction treatment with postoperative chemotherapy (5–7,9,20,21), and the latter has recently been associated with improved outcome, which may also bias the comparison (43).

In conclusion, our study demonstrates that surgery does not improve survival compared with chest radiotherapy in patients with unresectable stage IIIA-N2 lung cancer after response to induction chemotherapy. In view of its low morbidity and mortality, radiotherapy is to be considered the preferred locoregional treatment for these patients. Properly designed studies to

investigate whether surgery has a role in patients with confirmed mediastinal clearance are needed.

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Notes

List of institutions and investigators in descending order of their respective accrual (in rounded %) to the 332 randomly assigned patients:

Free University Medical Center, Amsterdam, The Netherlands (E. F. Smit, G. Giaccone, J. van Mourik, P. Postmus): 11; Erasmus Medical Center, Rotterdam, NL, (T. A. W. Splinter, A. Maat, S. Senan, M. de Jonge, J. P. v. Meerbeeck): 9; St Antonius Ziekenhuis, Nieuwegein, NL (F. Schramel): 8; Anhems Radiotherapeutisch Instituut, NL (G. W. P. M. Kramer, H. Smit, S. Gans): 6; Radboud University Medical Center, Nijmegen, NL (J. Festen, V. C. Tjan-Heijnen, J. Termeer): 6; Jeroen Bosch Ziekenhuis, 's Hertogenbosch, NL (B. Biesma): 6; Netherlands Cancer Institute, Amsterdam, NL (N. v. Zandwijk, P. Baas, J. Belderbos): 5; Leids Universitair Medisch Centrum, Leiden, NL (L. Willems): 5; Universitair Ziekenhuis Gasthuisberg, Leuven, B (J. Vansteenkiste, P. de Leyn): 4; Universitair Medisch Centrum Utrecht, Utrecht, NL (N. Schlösser, S. Y. Elsharouni): 4; Universitair Ziekenhuis Antwerpen, Edegem, B (P. E. Y. V. Schil, J. P. v. Meerbeeck): 3; Isala Klinieken, Zwolle, NL (J. Stigt): 3; Algemeen Ziekenhuis Middelheim Antwerp, B (D. Galdermans, K. Goor, P. De Roover): 2; OnzeLieve Vrouwe Gasthuis, Amsterdam, NL (B. Kwa): 2; Algemeen Ziekenhuis St Jan, Brugge, B (D. Van Renterghem): 2; Klinicni Center, Golnik, SL (A. Debeljak): 2; Université Catholique de Louvain, Mont Godinne, Yvoir B (L. Delaunois): 2; Royal Marsden Hospital, Sutton, U.K. (I. Smith, M. O'Brien, P. Goldstraw): 2; Ospedale SL Gonzaga, Torino, I (G. Scagliotti): 1; Spaarne Ziekenhuis, Haarlem, NL (H. van Breukelen): 1; National Cancer Institute, Genoa, I (A. Ardizzoni): 1; Slotervaartziekenhuis, Amsterdam, NL (P. van Spiegel): 1; Maria Sklodowska-Curie Medical Cancer Center, Warsaw, PL (M. Krzakowski): 1; Lievensberg Ziekenhuis, Bergen op Zoom, NL (H. Liem), Franciscusziekenhuis, Roosendaal, NL (A. van Boxem), UZGent, Gent, B (P. Pinson, G. Joos), Weston Park Hospital, Sheffield, U.K. (M. Hatton), Royal Infirmary, Leicester, U.K. (K. O'Byrne), Policlino Monteluce, Perugia, I (S. Darwish), Clinique Sainte-Elisabeth, Namur, B (A. Baudoux), Algemeen Ziekenhuis Zusters Barmhartigheid, Ronse, B (J. Verschuere), CHR-St Jozeph, Mons, B (JP d'Odemont), Istituto Nazionale, Napoli, I (C. Gridelli), Elkerliek Ziekenhuis, Helmond, NL (P. van Valenberg), Ziekenhuis De Heel, Zaandam, NL (A. van Bochove), Leyenburg Ziekenhuis, Den Haag, NL (E. Lammers), Hopital de Jolimont, Haine St Paul, B (M. Beauduin), Twee Steden Ziekenhuis, Tilburg, NL (H. Goey), Western General Hospital, Edinburgh, U.K. (A. Price), Algemeen Ziekenhuis Hoge Beuken, Antwerpen, B (W. Moorkens), Stedelijk Ziekenhuis, Roeselare, B (W. Verbeke): all lesser than 1.

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