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ORIGINAL REPORT

Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

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ABSTRACT

Purpose
Concurrent chemoradiotherapy with or without surgery are options for stage IIIA(N2) non–small-cell lung cancer. Our previous phase II study had shown the efficacy of induction chemotherapy followed by chemoradiotherapy and surgery in patients with IIIA(N2) disease and with selected IIIB disease. Here, we compared surgery with definitive chemoradiotherapy in resectable stage III disease after induction.

Patients and Methods
Patients with pathologically proven IIIA(N2) and selected patients with IIIB disease that had medical/functional operability received induction chemotherapy, which consisted of three cycles of cisplatin 50 mg/m^2 on days 1 and 8 and paclitaxel 175 mg/m^2 on day 1 every 21 days, as well as concurrent chemoradiotherapy to 45 Gy given as 1.5 Gy twice daily, concurrent cisplatin 50 mg/m^2 on days 2 and 9, and concurrent vinorelbine 20 mg/m^2 on days 2 and 9. Those patients whose tumors were reevaluated and deemed resectable in the last week of radiotherapy were randomly assigned to receive a chemoradiotherapy boost that was risk adapted to between 65 and 71 Gy in arm A or to undergo surgery (arm B). The primary end point was overall survival (OS).

Results
After 246 of 500 planned patients were enrolled, the trial was closed after the second scheduled interim analysis because of slow accrual and the end of funding, which left the study underpowered relative to its primary study end point. Seventy-five patients had stage IIIA disease and 171 had stage IIIB disease according to the Union for International Cancer Control TNM classification, sixth edition. The median age was 59 years (range, 33 to 74 years). After induction, 161 (65.4%) of 246 patients with resectable tumors were randomly assigned; strata were tumor-node group, prophylactic cranial irradiation policy, and region. Patient characteristics were balanced between arms, in which 81 were assigned to surgery and 80 were assigned to a chemoradiotherapy boost. In arm B, 81% underwent R0 resection. With a median follow-up after random assignment of 78 months, 5-year OS and progression-free survival (PFS) did not differ between arms. Results were OS rates of 44% for arm B and 40% for arm A (log-rank $P = .34$) and PFS rates of 32% for arm B and 35% for arm A (log-rank $P = .75$). OS at 5 years was 34.1% (95% CI, 27.6% to 40.8%) in all 246 patients, and 216 patients (87.8%) received definitive local treatment.

Conclusion
The 5-year OS and PFS rates in randomly assigned patients with resectable stage III non–small-cell lung cancer were excellent with both treatments. Both are acceptable strategies for this good-prognosis group.

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INTRODUCTION

In 2012, approximately 1.8 million people worldwide received a diagnosis of lung cancer.[1] More than 85% of these occurrences were non–small-cell lung cancer (NSCLC) histopathologies.[2] Approximately 30% of patients are in stage III according to the new Union for International Cancer Control (UICC) TNM classification, seventh edition.[2] Patients with stage III disease with good performance status and without relevant comorbidities will receive concurrent chemoradiotherapy as treatment with curative intent.[3,4] Data from several randomized phase III trials and a meta-analysis based on individual patient data have confirmed 5-year survival rates between 10% and 20% after concurrent chemoradiotherapy protocols for stage III NSCLC.[5] After two large prospective randomized trials, arguments remain to perform surgical resection after induction therapy in selected patients with IIIA(N2) disease. Nevertheless, it is not clear if this will affect overall survival (OS) compared with curative radiation alone.[5-9] The EORTC (European Organization for Research and Treatment of Cancer) trial included patients with proven stage IIIA(N2) disease but was not able to substantiate a benefit for surgery in patients who experienced disease response versus single-modality radiotherapy at curative doses after three cycles of induction chemotherapy.[6] Investigators in the Intergroup trial selected patients with any proof of N2 disease (IIIA-N2) and randomly assigned the patients to induction concurrent chemoradiotherapy plus surgery versus definitive chemoradiotherapy with radiation doses of 61 Gy.[9] This trial, although not positive for surgery in its primary end point OS, showed a significant benefit in progression-free survival (PFS) and suggested some benefit after lobectomy as surgical intervention.[8,9] In addition to the researchers who conducted these trials that were aimed exclusively at stage IIIA(N2) disease, our group—after long-term experience with trimodality treatment of stage III disease—piloted a complex induction protocol with three cycles of cisplatin and paclitaxel and concurrent chemoradiotherapy with 45 Gy, hyperfractionated-accelerated radiotherapy followed by surgery. This multicenter, phase II pilot trial demonstrated encouraging long-term survival also in selected patients with stage IIIB disease after surgery as part of our trimodality approach.[10-12] Given this background, in 2004, we started a multicenter, phase III trial in high-volume thoracic centers to investigate surgery versus a definitive concurrent chemoradiotherapy boost in patients after our complex induction protocol.[13] Here, we present final results of the survival end points for this multicenter, phase III, randomized trial.

PATIENTS AND METHODS

Patients

Patients with pathologically proven NSCLC who had a good Eastern Cooperative Oncology Group performance status of 0 or 1 were included. Patients must have had less than 10% weight loss in the 6 months before diagnosis. Adequate renal, hepatic, and hematologic functions were prerequisites. Patients had to have had potentially resectable stage IIIA(N2) or selected IIIB disease according to the UICC TNM classification, sixth edition.[14] N2 disease had to be pathologically proven during mediastinoscopy (recommended), endobronchial ultrasonography, or parasternal mediastinotomy. Selected resectable IIIB disease was defined as N3 disease with contralateral mediastinal nodes and proven T4 disease with involvement of the pulmonary artery, carina, left atrium, vena cava, or mediastinum. Positron emission tomographic (PET) or PET–computed tomographic staging, which was performed in 97%, and brain imaging investigations were routinely recommended. Cardiopulmonary status investigations had to include complete lung function testing, including assessment of diffusing capacity of the lung for carbon monoxide, ventilation-perfusion scanning, stress electrocardiography, and echocardiography for adequate assessment of functional operability. Criteria are described in the Appendix, online only.

This trial, including dose-escalated radiotherapy, was approved by ethics committees of all participating institutions and by the German Federal Office for Radiation Protection. Written informed consent was obtained from all patients who entered on this study.

Study Design

Induction chemotherapy consisted of three cycles of dose-dense cisplatin and paclitaxel in a 21-day cycle. Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week. The minimum interval between daily fractions was 6 hours. Three-dimensional treatment planning was mandatory. Intensity-modulated radiotherapy was not allowed. Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m^2 on days 2 and 9 and vinorelbine 20 mg/m^2 on days 2 and 9 of neoadjuvant radiotherapy. Definitive boost radiotherapy was given at 2 Gy per fraction, five fractions per week, to a cumulative dose of 20 to 26 Gy without a treatment break from neoadjuvant radiotherapy. A 26-Gy boost dose was recommended if deliverable within the normal tissue constraints. Specific radiation parameters, techniques, concurrent chemotherapy application given to the boost (cisplatin 40 mg/m^2 on day 2 and vinorelbine 15 mg/m^2 on days 2 and 9 of the boost radiotherapy), and the specific radiation boost application are described in detail in the protocol in the Appendix. The maximum allowed mean dose to the lung was 18 Gy, and the maximum dose at the spinal cord had to be less than 42 Gy. To avoid increased toxicities during the concurrent chemoradiotherapy boost, and given the previous experience in the pilot phase II study, concurrent chemotherapy to the boost was reduced in doses of cisplatin and vinorelbine.

Patients were reassessed during the last week of concurrent chemoradiotherapy. If their disease was reconfirmed to be functionally and technically resectable by the multidisciplinary tumor board, random assignment to both trial arms was performed by means of central random assignment at the statistical center at Essen University Hospital.

Statistical Analysis

The alternative H1 hypothesis of this study was that a 5-year OS rate of 25% after random assignment in arm A and a 5-year OS rate of 40% in arm B corresponded to a hazard ratio of 0.67. The expected OS rate in arm B was based on data from our pilot phase II study.[11] No difference in survival was assumed under the H0 hypothesis. The primary end point was OS, and the secondary end point was PFS. For a type I error of $\alpha = .05$ and a type II error of $\beta = .20$, the number of randomly assigned patients needed was 300. Stratified random assignment was performed according to the method by Zelen by using the following strata: tumor-node subgroup (ie, T1-3, N2; T4, N0-1; selected T1-3, N3; or T4, N2); intended prophylactic cranial irradiation treatment (ie, yes or no); and country of participating institution (ie, Germany or other countries).[15] Random treatment allocation was obtained from the Department of Biostatistics, University Hospital Essen, within 24 hours after submission of the random assignment form; this included interdisciplinary tumor board evaluation. Two interim analyses of efficacy and toxicity were preplanned at 35 and 70 deaths. Continuous toxicity monitoring by an independent data safety monitoring committee was implemented with rigidly predefined stopping rules. Follow-up visits were scheduled every 3 months after random assignment. Either physical examination plus chest radiography or computed tomography was mandatory at each visit. OS was defined as the time from random assignment to death as a result of any cause. PFS was defined as the time from random assignment to local or distant relapse or death as a result of any cause. Progression on imaging studies was evaluated according to World Health Organization criteria.[16] Survival curves were compared by applying a stratified, two-sided, log-rank test by using Proc LIFETEST (SAS statistical software, version 9.4; SAS Institute, Cary, NC).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Arm A: Definitive CT/RT (n = 80)		Arm B: Surgery (n = 81)		Patients Not Randomly Assigned (n = 85)		All Patients (N = 246)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median (range)	59 (42-74)		58 (33-72)		59 (41-73)		59 (33-74)	
< 60	41	51	46	57	43	51	130	53
≥ 60	39	49	35	43	42	49	116	47
Sex								
Male	53	66	56	69	67	79	176	72
Female	27	34	25	31	18	21	70	28
ECOG performance status								
0	60	75	60	74	50	59	170	69
1	20	25	21	26	34	40	75	30.5
2	0	0	0	0	1	1	1	0.5
Histology								
Adenocarcinoma	40	50	36	44.5	31	36	107	43.5
Squamous cell carcinoma	28	35	35	43	32	38	95	38.5
Large cell	7	9	4	5	11	13	22	9
Mixed or other	5	6	6	7.5	11	13	22	9
Tumor-node group								
T4, N0 or N1	28	35	24	30	28	33	80	32.4
T1-3, N2	26	32.5	29	36	20	23.5	75	30.5
T1-4, N3 or T4, N2	26	32.5	28	34	37	43.5	91	37
Stage								
IIIA	26	32.5	29	36	20	23.5	75	30.5
IIIB	54	67.5	52	64	65	76.5	171	69.5
PCI policy								
Planned or already performed	21	26	21	26	NA		NA	
Not planned or not proposed	59	74	60	74	NA		NA	
Region								
Germany	79	99	80	99	NA		NA	
Other countries	1	1	1	1	NA		NA	

Abbreviations: CT/RT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not available; PCI, prophylactic cranial irradiation.

Strata were those from the random assignment. The assumption of proportional hazards in treatment groups was analyzed by the Proc PHREG (SAS statistical software). A detailed description of the futility analysis appears in the Appendix.

Because ESPATUE remained underpowered in its primary end point, we also combined results from the North American Intergroup Trial and results from ESPATUE by using a Bayesian approach.[17]

RESULTS

Accrual started in January 2004 and stopped in January 2013 with 246 patients. The number of patients enrolled was lower than initially projected. Interim analyses were performed according to the protocol at 35 events in 2005 and at 70 events in 2012, but no stopping criteria for toxicity or efficacy end points were met, as evaluated by an independent data-monitoring committee. At the end of 2012, investigators decided after consultation with the independent data-monitoring committee, to stop the study on January 31, 2013, because of slow accrual and to allow for a 1-year minimum for additional follow-up before final analysis. Given this recruitment, which was less than originally planned, the study remained underpowered.

Patient Characteristics

Characteristics of all 246 recruited patients are presented in Table 1. and Appendix Table A1, online only. Seventy-five patients had stage IIIA-UICC6 disease, and 171 had stage IIIB-UICC6 disease. No significant differences were noted in patient characteristics between randomly assigned arms or in the comparison to the patient group that was not randomly assigned (Table 1 and Appendix Table A1, online only).

Treatment Compliance

Figure 1 shows the CONSORT diagram for all patients included on the study. Of 246 recruited patients, 237 received the planned three cycles of induction chemotherapy, and 227 patients completed induction chemoradiotherapy according to protocol. Overall, 161 (65.4%) of 246 patients underwent final random assignment. Seventy-six patients received the assigned, planned boost chemoradiotherapy. Three patients chose surgery, and one patient died as a result of a pulmonary embolism while receiving treatment at a cumulative radiotherapy dose of 51 Gy.

The median time between induction treatment and boost was 0 days (range, 0 to 7 days). Eight patients had a break longer than 2 days. Of 81 patients randomly assigned to arm B, 70 underwent surgery.

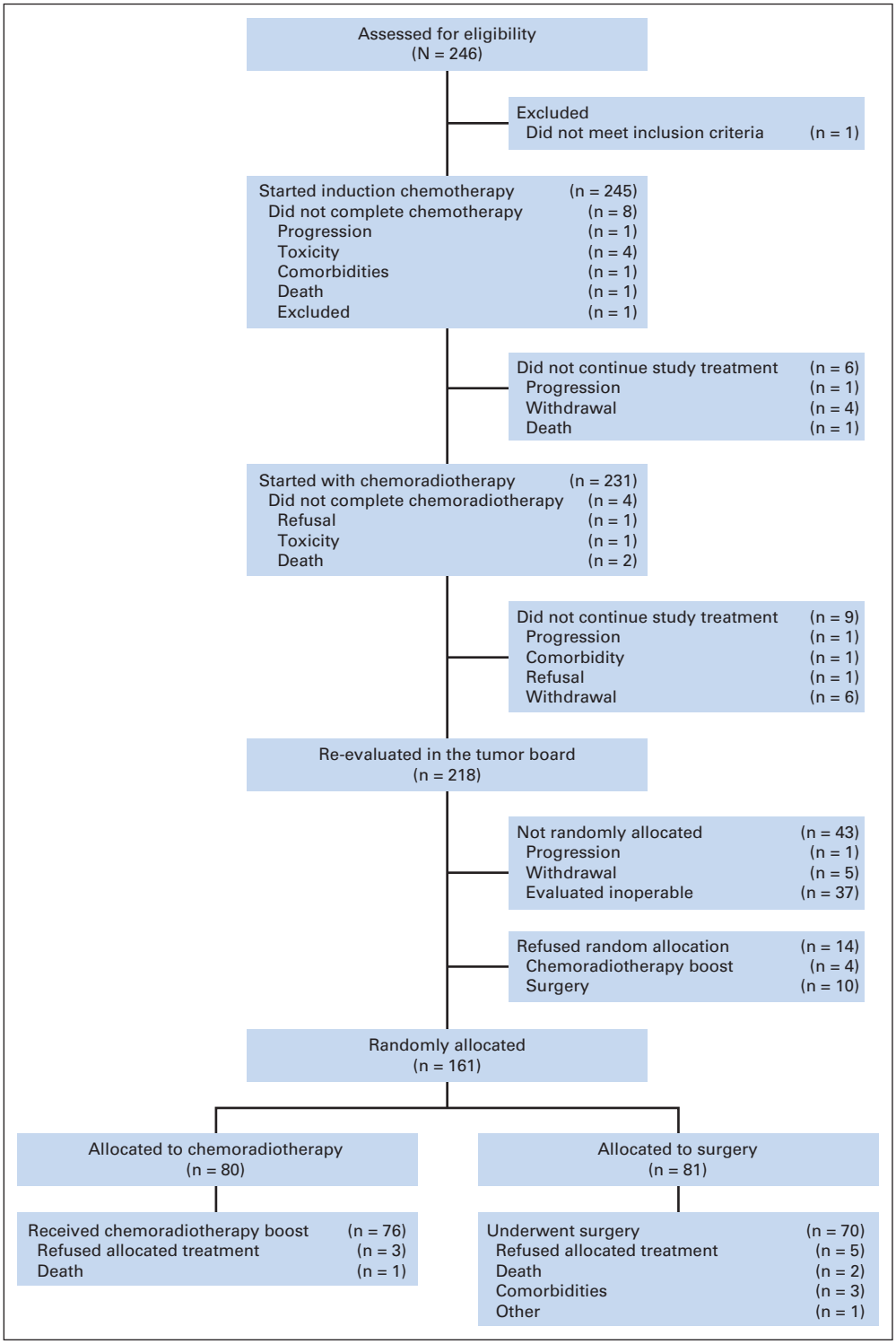

Fig 1. CONSORT diagram.

After random assignment, four patients refused surgery and received a chemoradiotherapy boost without a break. Four additional patients received a boost of 18 to 26 Gy after a break of 39 to 85 days; three of them had functionally inoperable disease at the time of planned thoracotomy, and one refused surgery. One patient with persistent N3 disease observed during repeat mediastinoscopy did not receive additional treatment. Two patients died after random assignment before planned surgery; causes were newly diagnosed brain metastases and cardiac arrest that resulted from a known heart-rhythm disorder.

Surgical Treatment

Of 70 patients who received surgery in arm B, the resection status was R0, R1, and R2 in 66, three, and one patients, respectively. Median time from the last day of radiotherapy till surgery was 37 days (range,

Table 2. Maximum Toxicities Observed in All Patient Groups

	Arm A: Definitive CT/RT (n = 80)						Arm B: Surgery (n = 81)						Patients Not Randomly Assigned (n = 85)						All Patients (N = 246)					
	Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5		Grade 3		Grade 4		Grade 5	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Leukopenia	35	44	13	16	0	0	40	49	9	11	0	0	26	31	6	7	0	0	101	41	28	11	0	0
Anemia	7	9	0	0	0	0	10	12	0	0	0	0	2	2	0	0	0	0	19	8	0	0	0	0
Thrombocytopenia	6	8	2	3	0	0	8	10	1	1	0	0	3	4	1	1	0	0	17	7	4	2	0	0
Nausea/vomiting	7	9	0	0	0	0	10	12	1	1	0	0	3	4	0	0	0	0	20	8	1	< 1	0	0
Neuropathy	5	6	0	0	0	0	5	6	0	0	0	0	4	5	2	2	0	0	14	6	2	1	0	0
Esophagitis	21	26	0	0	0	0	11	14	0	0	0	0	9	11	1	1	0	0	41	17	1	< 1	0	0
Mucositis/stomatitis	2	3	0	0	0	0	3	4	0	0	0	0	2	2	0	0	0	0	7	3	0	0	0	0
Pulmonary	3	4	1	1	1	1	3	4	1	1	5	6	7	8	3	4	2	2	13	5	5	2	8	3
Other GI or renal	5	6	0	0	0	0	7	9	1	1	0	0	9	11	1	1	0	0	21	9	2	1	0	0
Cardiac	2	3	0	0	0	0	4	5	0	0	0	0	3	4	1	1	2	2	9	4	1	< 1	2	1
Miscellaneous infection	1	1	1	1	1	1	7	9	0	0	0	0	3	4	2	2	2	2	11	4	3	1	3	1
Fatigue	8	10	0	0	0	0	5	6	0	0	0	0	4	5	0	0	0	0	17	7	0	0	0	0
Pain	16	20	0	0	0	0	19	23	0	0	0	0	13	15	0	0	0	0	48	20	0	0	0	0

Abbreviation: CT/RT, chemoradiotherapy.

20 to 61 days). Pneumonectomies were performed in 23 of 70 patients, and bilobectomies, lobectomies, and segmentectomies were performed in seven, 39, and one patients, respectively. Additional resections involved the intrapericardial region, diaphragm, chest wall, bronchial sleeve, vascular sleeve, major vessel, esophageal area, or vertebral body in 45 patients. All patients underwent routine mediastinal lymphadenectomy. Pathologic complete responses (pCR) based on resected specimen data were observed in 27 (33%) of 81 randomly assigned patients.

Treatment Toxicity

Maximum treatment-related toxicities observed in all 246 patients are shown in Table 2. All toxicities of grades 3 and 4 in both randomly assigned arms were not unexpected and could be considered acceptable. The toxicity distribution in the two study arms was balanced and also was balanced compared with the group of patients not randomly assigned. Two patients died during the protocol before random assignment, probably because of therapy-related reasons: one died after the third chemotherapy cycle at home, and the other died as a result of sepsis during induction chemoradiotherapy. Also, seven patients died after random assignment, probably because of treatment-related causes: two patients in arm A died during definitive chemoradiotherapy (one from pneumonia after neutropenia; the other as a result of pneumonia and multiorgan failure). Of five patients in the surgical arm, three died as a result of lung bleeds, and two died as a result of pneumonia and empyema. All died greater than 30 days after thoracotomy. Four of the five patients with events in the surgical arm underwent lobectomy, one further underwent bilobectomy, two had additional chest-wall resections, one received an intrapericardial resection, and one had a bronchial-sleeve resection. None of the postsurgical deaths was noted in a patient after pneumonectomy (Table 3). Four patients who were not randomly assigned died after induction chemoradiotherapy, and these were probably treatment-related deaths: two died after definitive chemoradiotherapy with respiratory failure and myocardial infarction, and two died as a result of pneumonia after surgery.

Outcome

By incorporating the strata, as in the log-rank test, the proportional hazards assumption was accepted with $P = .34$ for OS and $P = .21$ for PFS. OS from the time of random assignment as the major end point was not significantly different between treatment arms (Fig 2; $P = .34$, stratified log-rank test). The 5-year OS rate in arm A was 40% (95% CI, 29% to 52%) and was 44% (95% CI, 32% to 56%) in arm B. Median follow-up after random assignment was 78 months. PFS was comparable in both arms, as shown in Figure 3 ($P = .75$, stratified log-rank test). PFS reached a plateau at approximately 36 months in both arms. The 5-year PFS rate in arm A was 35% (95% CI, 25% to 46%) and was 32% (95% CI, 22% to 43%) in arm B. Of 80 patients in

Table 3. Surgical Procedures and Maximum Postoperative Toxicity Observed in Arm B

	No. of Toxicities by Grade in Arm B (surgery; n = 70)		
Toxicity by Procedure	Grade 3	Grade 4	Grade 5
Lobectomy (n = 39)			
Anemia	2	0	0
Pulmonary	3	0	4
Other GI or renal	1	0	0
Cardiac	3	0	0
Miscellaneous infection	2	0	0
Pain	6	0	0
Pneumonectomy (n = 23)			
Anemia	3	0	0
Cardiac	1	0	0
Miscellaneous infection	1	0	0
Pain	5	0	0
Bilobectomy (n = 7)			
Anemia	1	0	0
Pulmonary	0	0	1
Segmentectomy (n = 1)			
Other GI or renal	1	0	0

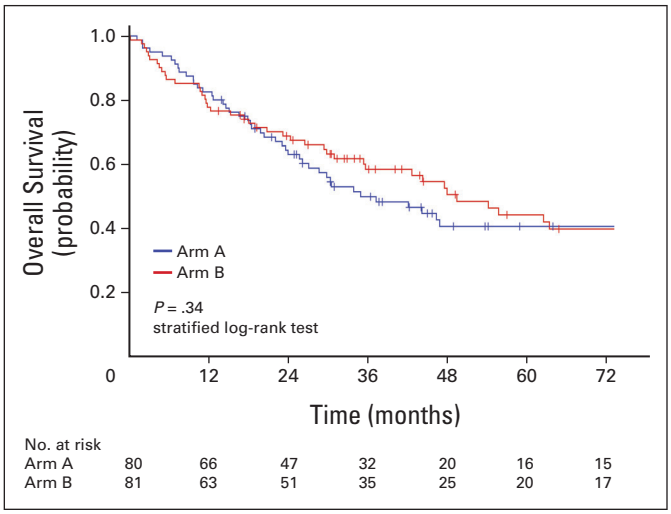

Fig 2. Overall survival of randomly assigned arms.

arm A, 47 died, and six experienced progression without death during follow-up; in arm B, of the 81 patients total, 43 died, and 12 experienced progression without death during follow-up. The 5-year OS for all 246 initially recruited patients for entry onto this trial was 34.1% (95% CI, 27% to 41%; Appendix Fig A1).

DISCUSSION

This randomized, phase III trial for resectable stage IIIA(N2) and selected IIIB NSCLC was performed in centers with long-standing experience with multidisciplinary approaches, including surgery.[18] We could not substantiate a benefit in the 5-year OS rate for surgery versus individually dose-escalated chemoradiotherapy after induction chemotherapy and concurrent chemoradiotherapy. Also, no improvements in the median OS, median PFS, or 5-year PFS rate were observed. Both interventions showed acceptable toxicities, which was in line with data reported in the literature.[4-6,9,10,19-22] Patients on our trial included approximately one third who had pathologically proven

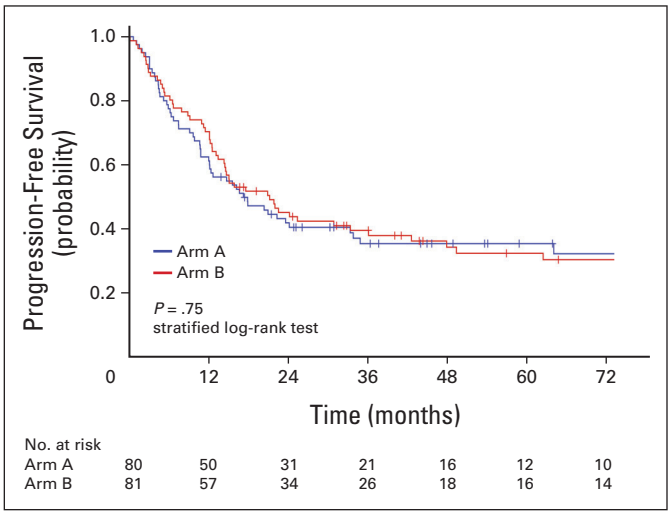

Fig 3. Progression-free survival of randomly assigned arms.

IIIA(N2) disease; one third who had stage T4, N1 (formerly IIIB-UICC6 and now stage IIIA-UICC7); and approximately one third who had either T4, N2 or any proven N3 disease (now both stage IIIB-UICC7).[2,14]

The 5-year-OS data in randomly assigned patients from our trial are among the best reported so far from prospective trials with definitive chemoradiotherapy.[4-10,22,23] Whether these results are in part related to stage migration related to patient selection in our trial (no weight loss, PET–computed tomographic and magnetic resonance imaging of the brain) cannot be completely ruled out. However, using a similar schedule of hyperfractionated-accelerated radiotherapy and concurrent cisplatin/vinorelbine, the Maastricht group, with shorter median follow-up, observed comparable 2-year survival rates, which leaves the impression that this schedule is particularly effective.[24] Moreover, findings in the trimodality arm validate results from our previous single-center and multicenter experiences with this multimodality strategy.[10-12] To exclude as few patients as possible from random assignment, the predefined selection criteria broadly allowed inclusion of patients with potentially resectable disease, but we randomly assigned only those patients whose disease was reassessed as resectable after induction. Therefore, final patient selection depended on both initial tumor extension and response to induction.

One large, randomized trial of neoadjuvant concurrent chemoradiotherapy also previously failed to demonstrate benefit with surgery versus definitive radiotherapy/chemoradiotherapy in stage III for an OS end point.[6,9] The Intergroup trial investigators performed upfront random assignment of patients to induction chemoradiotherapy followed by surgery or to a definitive chemoradiotherapy protocol.[9] Patients on that study included patients with resectable tumors and any pathologic proof of N2 disease. Although no OS benefit for surgery was noted, PFS significantly improved with surgery. Results of unplanned matched-pair analysis suggested some benefit in OS after lobectomy. This study group also reported a high treatment-related death rate after right-sided pneumonectomy. In contrast, pneumonectomy-induced toxicity data from European high-level thoracic centers have shown reduced treatment-related mortality rates in centers with long-standing experience in multimodality protocols.[18,25] Despite the fact that the latter trial[9] included only stage IIIA(N2) disease, whereas two thirds of patients on our study had stage IIIB-UICC6 disease (which included stage groups T4, N0-1 and IIIB based on either T4 or N3), it is the trial most closely related to ours. To borrow strength for comparison between trimodality and chemoradiotherapy from the Intergroup trial with ESPATUE, we used a Bayesian approach.[17] Even if one assumes no heterogeneity between the trials, the posterior probability of the hypothesis of no difference between treatment arms in the primary OS outcome being true remained > 0.13. Therefore, superiority of trimodality in OS could not be substantiated.

The EORTC0841 trial had a different design. Patients had to have initial proof of any stage IIIA(N2) disease and had to have undergone induction treatment with three cycles of chemotherapy.[6] Those responding with complete, partial, or minor response after the third cycle were randomly assigned between surgery and single-modality radiotherapy. No significant differences were noted between arms in terms of OS and PFS. Treatment toxicities were acceptable in both arms, and no major perioperative problems were reported. After induction chemotherapy, 332 (57%) of 579 patients were randomly

assigned. In contrast to the Intergroup trial, this trial had no standard concurrent chemoradiotherapy as the comparison.

A third large, multicenter randomized study of stage IIIA(N2) disease was presented at the 2013 American Society of Clinical Oncology and 2014 European Society for Medical Oncology meetings.[26,27] The Swiss Group for Clinical Cancer Research randomly assigned patients with proven IIIA(N2) to induction chemotherapy with three cycles of cisplatin/docetaxel followed by surgery versus induction chemotherapy sequentially followed by 44 Gy of radiation and surgery. The primary end point of that study was OS. However, most patients had non-bulky lymph nodes < 5 cm. In that patient selection, no significant benefit in OS or event-free survival was noted for the inclusion of preoperative single-modality radiotherapy compared with induction chemotherapy alone. That trial was powered to detect a hazard ratio of 0.67; therefore, it remained insensitive to smaller differences in survival between arms. Both treatment arms showed excellent long-term survival; this finding was in line with other results reported for induction treatment with cisplatin/taxane.[10,28]

Several groups have tried to develop surrogate end points for local, locoregional, or systemic efficacy of induction strategies. Typically, achievement of pCR in mediastinal nodes after induction has significant effect on survival prognosis.[9,28] To compare induction protocols, local efficacy can also be evaluated by assessing the pCR rate in primary and lymph nodes at the time of surgery.[29] If we compare primary tumor data from the four randomized trials to data from our trial, the EORTC had a 5% pCR rate with induction chemotherapy; the Swiss trial had an 11.7% pCR rate with induction chemotherapy and a 16.2% pCR rate with induction chemotherapy and sequential radiotherapy; the Intergroup trial had a pCR rate of 14.4% with induction chemoradiotherapy; and our study had a pCR rate of 33% with complex induction chemotherapy and concurrent hyperfractionated chemoradiotherapy. The general pattern in all trials reveals that those with induction chemoradiotherapy show local/locoregional efficacy greater than the ones with chemotherapy and sequential radiation as induction therapy or those with induction chemotherapy alone. If these differences in local control can finally translate into improved OS remains to be determined. Of note, the complex induction used in our study demonstrated the highest pCR rate so far.

Our study included cisplatin/taxane-based induction before dose-dense concurrent chemoradiotherapy. Other investigations, which mostly involved carboplatin doublets, could not demonstrate a positive effect of induction chemotherapy within this combined-modality setting.[30] The extensive experience with cisplatin-based induction in our group and the high pCR rates at surgery leave the impression that such an approach is, at least, not harmful within such a complex treatment.

In conclusion, both trimodality treatment that includes surgery and bimodality treatment without surgery but with a definitive chemoradiotherapy boost lead to excellent long-term OS and PFS. In our patients, who included those with resectable stage IIIA(N2) or selected stage IIIB NSCLC, we observed 5-year OS rates greater than 40%, an acceptable toxicity profile, and moderate treatment-induced events when performed in high-level multimodality treatment centers.

To establish adjuvant chemotherapy after compete resection in NSCLC, a meta-analysis with 4,000 patients is necessary.[31] Currently, we do not have comparable trials that involve large numbers of patient to look at the value of surgery after induction. Therefore, after our randomized trial, both trimodality therapy that includes surgery and bimodality therapy without surgery remain valuable options for patients with stage III disease in whom surgery is potentially considered after the initial work-up. Well-established options with clearly comparable predictive factors for effectiveness and toxicity are needed to additionally optimize the treatment decision in individual patients. To further optimize the treatment decision in the individual patient, establishing predictive factors for effectiveness and toxicity would be of help and significant clinical relevance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

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Appendix

Clinical Trial Progress

The trial received approval from the ethics committee from the leading trials center on July, 3, 2003. Protocol version 1 was activated in the following months. From then onward, the study was sequentially initiated at five different centers. The first patient was accrued to the trial on January 14, 2004. The first patient was randomly assigned on March 31, 2004. A total of 125 patients were entered onto the clinical trial at five centers: four in Germany and one in the Netherlands. After patient accrual, a detailed patient-by-patient evaluation of serious adverse event toxicity and trials progress was done by an independent data safety monitoring committee (DSMC). On the basis of recruitment data and the available surgical resection data, the DSMC recommended an amendment to the protocol with some important changes. The DSMC proposed a focus on the patient inclusion, explicitly a focus on potentially resectable stage IIIA(N2) and selected IIIB disease at the time of enrollment so that the patient selection for random assignment at the end of neoadjuvant treatment might prevent fewer patients from being randomly assigned. Patients with diffuse mediastinal involvement and T4N3 tumors were explicitly excluded. The investigators revised the study protocol accordingly and submitted the amended trials protocol number two to the ethics committee for approval. The ethics committee granted approval of the amendment on February 14, 2008. With the active amended protocol number two, recruitment to the trial was restarted; from then on, 119 additional patients were recruited until August 23, 2012. Overall, 81 of the 127 patients recruited before and 80 of the 119 patients recruited after the protocol amendment were randomly assigned ($P = .57$, χ^2 test). The last patient was randomly assigned on November 23, 2012.Given the slower-than-expected patient accrual and the longer follow-up, the Central Statistical Center negotiated together with the DSMC and the trials investigators to perform a futility analysis described in this Appendix. On the basis of their recommendation, trials recruitment was stopped on January 31, 2013. The statistical redesign of the study proposed a 1 year of additional follow-up, and the final data cutoff was on January 31, 2014. All trials centers were contacted to proceed with study follow-up of the patients on the trial and to continue follow-up until this time point. Contact information and data about relapses or events in patients still at risk were requested between December 2013 and January 3014, with information about patients at risk as close as possible to the data cutoff of January 31, 2014. The data presented here represent this analysis from the data cutoff point given.

This final analysis was presented as a poster discussion paper that described the overall survival data information at the 50th Annual Meeting of the American Society of Clinical Oncology in 2014 in Chicago (Eberhardt WEE, et al: J Clin Oncol 32:5S, 2014 [suppl; abstr 7510]). The progression-free survival data were presented as an oral presentation at the Meeting of the American Society for the Treatment with Radiation Oncology in San Francisco in 2014 (Stuschke et al: Int J Radiat Oncol BiolPhys 90:S146-S147, 2014).

Futility Analysis

In addition to the tests of differences in efficacy between arms, a futility analysis was performed for overall and progression-free survivals. Progression-free survival did not incorporate the effects of second-line treatments for relapses at single or multiple sites and was able to reveal differences between treatments at earlier times than overall survival in locally advanced NSCLC, as reported in 2013 by Mauguen et al.[8] The futility analysis was performed after a minimum follow-up of 1 year according to the Whitehead method. A design with a one-sided alternative was used. The type I error α level and type II error β level were .05 and .2, respectively. Survival or progression-free survival curves were compared by using the stratified log-rank test. The procedures SEQTEST, SEQDESIGN, and LIFETEST were used for this analysis (SAS software; SAS Institute, Cary, NC).The boundary for acceptance of the hypothesis of equal efficacy of both treatment arms was crossed for progression-free survival. For overall survival, this boundary was not crossed. The predictive power of this trial at full accrual of 300 randomly assigned patients given the current data was estimated to be 23%.

Proportional Hazard Analysis

Some indications existed for small deviations from the proportional hazard assumption for overall survival. The survival curve in the surgical arm showed more early deaths and later crossed the survival curve for the nonsurgical arm at 18 months, which indicates deviations from a proportional hazard assumption between arms. In arm B, the hazard at early time points ≤ 6 months after random assignment was by a ratio of 3.21 (95% CI, 1.014 to 19.18); this was larger than expected from the hazard function at later times > 6 months in arm B and arm A under the proportional hazard assumption ($P = .047$, χ^2 test). A similar crossing of the survival curves for the surgical and nonsurgical arms was observed in the trial reported in 2009 by Albain et al.[9] Proportional hazard analysis was performed by using the procedure PHREGSAS 9.4 (SAS Institute). However, a Komolgorov-type supremum test of the observed cumulative sum of a transform of the Martingale residuals over the follow-up time, with our incorporated strata used in the log-rank test, could not reject the proportional hazards assumption ($P = .34$).

No considerable indications occurred for deviations from the proportional hazard assumption for progression-free survival, as performed by using the procedure PHREG SAS 9.4 (SAS Institute; $P = .21$, Komolgorov-type supremum test that incorporated strata as in the log-rank test). The hazard ratio for progression-free survival was 1.06 (95% CI, 0.73 to 1.55) for patients in arm A versus arm B.

Table A1. Additional Patient Clinical Characteristics

Characteristic	Arm A: Definitive CT/RT (n = 80)		Arm B: Surgery (n = 81)		Patients Not Randomly Assigned (n = 85)		All Patients (N = 246)	
	No.	%	No.	%	No.	%	No.	%
Primary T stage								
T1	3	4	8	10	4	5	15	6
T2	27	34	23	28	17	20	67	27
T3	6	7	6	7	7	8	19	8
T4	44	55	44	54	57	67	145	59
Primary N stage								
N0	27	34	24	30	26	31	77	31
N1	1	1	0	0	2	2	3	1
N2	41	51	49	60	43	51	133	54
N3	11	14	8	10	14	16	33	13
Center								
Essen	57	71	58	72	68	80	183	74
Tübingen	18	23	22	27	16	19	56	23
Mainz	3	4	0	0	0	0	3	1
Maastricht	1	1	1	1	1	1	3	1
München	1	1	0	0	0	0	1	0.5
Lactate dehydrogenase level								
Normal	57	71	64	79	58	68	179	73
Abnormal	19	24	13	16	24	28	56	23
Not assessed	4	5	4	5	3	4	11	4
Median (range) FEV1, %	77 (25-107)		74 (40-126)		77 (30-121)		77 (30-126)	
No. of positive lymph node stations								
0	27	34	24	30	26	31	77	31
1	23	29	19	23	28	33	70	28
2	17	21	24	30	12	14	53	22
3	5	6	8	10	6	7	19	8
4	0	0	1	1	2	2	3	1
Unknown	8	10	5	6	11	13	24	10

Abbreviation: CT/RT, chemoradiotherapy.

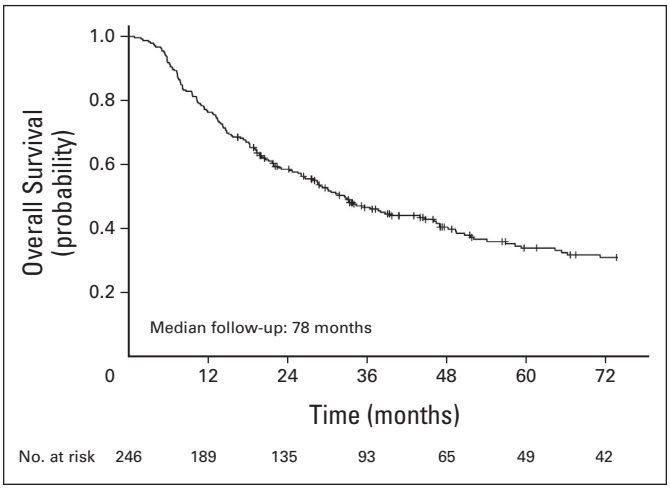

Fig A1. Overall survival of all recruited patients.