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Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer

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Abstract

Background—Data from meta-analyses support the use of induction or adjuvant platinum-based chemotherapy for locally advanced non-small cell lung cancers (NSCLCs). This phase 2 study assessed the role of induction cisplatin and docetaxel followed by surgery in patients with resectable stage I–III NSCLCs, followed by 12 months of adjuvant erlotinib.

Methods—Patients with resectable stage I–III NSCLCs received 3 cycles of cisplatin 80 mg/m2, docetaxel 75 mg/m2 every 21 days for 3 cycles, followed by surgery, followed by adjuvant erlotinib for 12 months. The primary endpoint included safety. Long-term efficacy outcomes and exploratory analysis of intermediary endpoints are also reported (NCT00254384).

Results—Forty-seven eligible patients received a median of 3 cycles of induction treatment, 37 underwent surgical resection, and only 21 received adjuvant erlotinib. Two patients died in the peri-operative period (1 sepsis during chemotherapy, 1 ARDS post-operatively). Most common grade 3–5 toxicities during chemotherapy included hypokalemia (8%), infection (7%), granulocytopenia (25%). During adjuvant erlotinib, 14% of patients experienced grade 2 rash. Median overall survival was 3.4 years. Major pathologic responses in the primary tumor were observed in 19% (7/37) of patients and correlated with improved long-term overall survival. Complete pathologic response in mediastinal/hilar nodes also correlated with superior survival.

Conclusions—Induction cisplatin and docetaxel was well tolerated. Adjuvant erlotinib did not improve outcomes compared to historical controls. Major pathologic response predicted for improved long-term survival and is a suitable intermediary endpoint for future phase 2 studies.

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Cisplatin-based adjuvant chemotherapy has become the standard of care treatment following surgical resection of patients with lymph node positive non-small cell lung cancer (NSCLC), based on data from 3 randomized controlled studies. (1–3) A meta-analysis including 4584 patients demonstrated a hazard ratio (HR) for death of 0.89 in favor of adjuvant chemotherapy, translating into an absolute improvement in 5-year overall survival (OS) of 5.4%.(4)

Small-scale studies evaluating the role of induction chemotherapy in patients with stage III NSCLC suggested a potential benefit from systemic therapy prior to surgery.(5, 6) Subsequent randomized phase III studies evaluated the effects of induction chemotherapy in patients with stage I–III NSCLC.(7–11) Although most of these trials did not individually demonstrate a clear benefit in OS from induction treatment, they showed that (1) induction treatment elicited objective responses in at least 40% of patients; (2) there was no significant increase in peri-operative mortality; (3) induction chemotherapy did not negatively impact disease resectability. Furthermore, a meta-analysis including 15 randomized trials demonstrated a HR for death of 0.87 in favor of induction treatment, translating into an absolute 5-year OS improvement of 5%.(12) Since these figures are similar to the benefits seen in the adjuvant chemotherapy meta-analysis, one could argue that chemotherapy, administered either before or after surgery, is a reasonable option in patients that are candidates for peri-operative systemic therapy. Unfortunately, the use of OS as primary endpoint in clinical trials of perioperative chemotherapy in resectable NSCLC patients is challenging in that these studies are prolonged and costly. We (13) and others (14) have demonstrated that the degree of pathologic tumor regression in resected specimens after neoadjuvant chemotherapy provides an objective criterion of response and correlates with long-term outcomes in patients with resectable NSCLC. The major pathologic response (MPR), defined as ≤10% viable tumor cells in resected tumors following induction chemotherapy, correlates with improved disease–free survival (DFS) and OS, and depicts the extent of survival benefit provided by the treatment. This pathologic criterion is being incorporated as a surrogate measurement of clinical benefit in studies testing novel agents in the neoadjuvant setting.

When this study was conceived, there were limited data on induction cisplatin-based combinations used as standard first-line therapies in metastatic disease, as well as on the role of integrating targeted agents to peri-operative systemic therapy. Therefore, we designed the present study to assess the role of induction cisplatin and docetaxel followed by surgery in patients with resectable NSCLC. After surgery, patients also received adjuvant erlotinib (an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor) for 12 months. We report the safety, the long-term clinical outcomes and the results of a comprehensive exploratory analysis of intermediary endpoints, including MPR as a surrogate of benefit induced by neoadjuvant chemotherapy.

Material and Methods

This was an open-label, single-arm, phase II trial conducted at The University of Texas M. D. Anderson Cancer Center, approved by the Institutional Review Board and conducted in

accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patient Eligibility

Inclusion criteria included: previously untreated, histologically confirmed diagnosis of surgically resectable stage I–III NSCLC (American Joint Committee on Cancer Staging Manual, 6th edition); ECOG performance status of 0–1; age ≥ 18 years; adequate bone marrow, liver, and renal function. Exclusion criteria included: uncontrolled intercurrent illness; pre-existing peripheral neuropathy grade ≥ 2; history of severe hypersensitivity reaction to docetaxel or polysorbate 80. The planned sample size was 50 patients.

Treatment Plan—Prior to study entry, all patients were required to sign an informed consent statement. Baseline evaluation included a CT scan of the chest to adrenals, a bronchoscopy with biopsies, as well as buccal smears and optional blood samples for correlative studies. Eligible patients were treated with cisplatin 80 mg/m^2 intravenously (IV) on day 1, docetaxel 75 mg/m^2 IV on day 1, every 21 days for 3 cycles. Granulocyte-colony stimulating factors were used at treating physician's discretion. Three weeks after cycle 3 of chemotherapy, a CT scan was repeated to assess treatment response. After 3 cycles of induction treatment, surgical resection was performed, followed or not by post-operative radiation therapy, at the physician's discretion. Within 90 days after surgery or post-operative radiation therapy, patients initiated erlotinib 150 mg orally daily for 12 months.

Study Endpoints and Statistical Analysis

The primary objectives of the study were to evaluate the safety of induction cisplatin and docetaxel followed by adjuvant erlotinib after surgical resection, and to evaluate biomarkers in buccal smears and lung tissue in response to erlotinib, as detailed in the Appendix. Unexpectedly, buccal smears and tumor tissue samples were not collected in most patients, since these were considered optional procedures per protocol. Therefore, the biomarker endpoint could not be analyzed. This report focuses solely on clinical outcomes data. Toxicities were recorded and graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.(15) DFS time was defined as the time from surgery to disease recurrence, development of a second primary lung cancer, or death, whichever occurred first (event), or last follow-up date (censor). Patients were followed up to 5 years after surgery. Time-to-event outcomes were estimated by the Kaplan-Meier method, and compared between subgroups of interest with the log-rank test.

Results

Patients

Between February 2, 2007 and June 3, 2009, 50 patients were enrolled in the study (3 patients did not meet all eligibility criteria and 47 patients were evaluable for analysis). Their baseline characteristics are described in Table 1. Stage I patients were enrolled based on preliminary results of the CALGB 9633 trial (16) that were available when our study was designed, demonstrating a significant survival benefit derived from adjuvant chemotherapy

in stage IB patients versus observation. Of the 15 patients with stage I, 7 had invasive mediastinal staging prior to treatment initiation, and all of them had disease negative mediastinal nodes (Supplemental Figure S1). Of the 32 patients with stage II (n=13) or III (n=19), 24 underwent invasive mediastinal/hilar staging prior treatment initiation and lymph node involvement was histologically confirmed in 13 patients (Supplemental Figures S2, S3).

Treatment

Treatment characteristics are presented in Table 2. Forty-seven patients initiated chemotherapy, and of these, 40 completed all 3 cycles of induction treatment. Ten patients never had a surgical resection due to early death during induction chemotherapy (1, due to non-neutropenic pneumonia after cycle 2 of treatment), development of metastatic disease (2), tumor deemed unresectable (3), and excessive cardiopulmonary risk (4). Seven of these patients received radiation (1) or concurrent chemo-radiation (6) after induction chemotherapy. Of the 37 surgically resected patients, 35 (95%) had a complete resection (R0) and 2 (5%) had positive microscopic margins (R1). The 90-day post-operative mortality was 3% (1 patient with lobectomy died of acute respiratory distress syndrome [ARDS]). Eight patients received post-operative radiation, 2 for positive margins and 6 for persistent post-induction mediastinal lymphadenopathy. There were only 3 out of 9 patients with persistent N2 disease after induction treatment that did not receive adjuvant radiation therapy. Following surgery (and post-operative radiation therapy, when appropriate), 16 patients did not receive adjuvant erlotinib, due to patient's choice (3), physician's choice (5), early progression (4), diagnosis of a second cancer (2), post-operative major complications (1), and early death (1). Of the 21 patients that initiated adjuvant therapy, 12 completed 12 months of treatment (Table 2).

Toxicity

The most common treatment-related adverse events (grades 2–5) during induction chemotherapy and adjuvant erlotinib are outlined in Tables 3 and 4, respectively. Surgical complications consisted of prolonged air leak (>5 days) in 7 patients, pneumonia (3), atrial fibrillation (3), recurrent laryngeal nerve palsy (1), deep vein thrombosis (1), hematoma requiring evacuation (1), and ARDS resulting in death (1). The peri-operative mortality rate was 4% (2/47; 1 pre- and 1 post-surgery).

Efficacy

Utilizing RECIST, among 47 patients who received induction chemotherapy, none exhibited a complete response (CR) to induction chemotherapy, 28 (60%) had a partial response (PR), 18 (38%) experienced stable disease, and only 1 (2%) experienced disease progression (PD). Pathologic CRs in both the primary tumor and nodes were uncommon (1, 3%). One of 16 patients with N0 disease pre-treatment (6%) who underwent surgery had lymph node involvement on surgical pathology (in the mediastinum, ypN2; Supplemental Figure S1). Of the 9 patients with N1 disease pre-treatment who underwent surgery, 8 (89%) remained N1 and 1 (11%) was downstaged to ypN0 at resection (Supplemental Figure S2). Of the 12 patients with pre-treatment N2 disease who underwent surgery, 4 (33%) had a pathologic CR

in the nodes (2 of these patients had histopathologically confirmed lymph nodes prior to treatment initiation) and 8 remained N2 at time of resection (Supplemental Figure S3).

We previously demonstrated that MPR to induction chemotherapy occurred in 19% of patients and was associated with improved long-term recurrence-free and overall survival. (13) The MPR rate in the 37 patients undergoing surgery in this study was also 19% (7/37 patients).

The median OS time from registration for the entire population (47) was 3.4 years (29 deaths). The 5-year OS for patients with pre-treatment stages I, II and III were 51.9%, 55.5% and 21.1%, respectively (Figure 1). With a median and maximum follow-up time of 5 years from surgery, 21 (57%) out of 37 surgically treated patients had disease recurrence and 2 (5%) developed a second primary lung cancer. The first site of recurrence was local in 1 patient, regional in 2 patients, distant in 11 patients, distant plus regional in 7 patients. The median OS time was not reached for patients that initiated erlotinib versus 2.3 years for those who did not (HR 3.26, 95% CI 1.36 – 7.85, from univariate Cox model, P=0.005 log-rank test).

Exploratory analysis

To leverage the detailed clinical annotation and uniform treatment in this cohort, we contrasted the associations of several intermediary endpoints with survival, including response by RECIST (PD or SD, versus PR); mediastinal downstaging (in patients with baseline N2 disease); hilar and mediastinal nodal pathologic CR (in patients with baseline N1 or N2 disease); and MPR in the primary tumor (in all surgically treated patients). While clinical response was not associated with improvements in DFS (Figure 2A) and OS (Figure 3A), hilar and mediastinal nodal CR was associated with a significant improvement in DFS in stage II and III patients (Figure 2C, P=0.04, log-rank test). A favorable response to treatment, as assessed by mediastinal downstaging, hilar and mediastinal nodal CR, or MPR in the primary tumor were all significantly associated with superior OS (Figure 3 B–D). While all 8 patients with stage III disease who did not have mediastinal downstaging died with a median OS time of 2.6 years, only 1 of 4 patients with nodal pCR died at 1. 4 years (Figure 3B, P=0.03, log-rank test). Among patients with stage II and III disease combined, 13 patients (among a total of 16) who did not experience nodal pCR died, while only 1 of 5 patients with nodal pCR died (Figure 3C, P=0.04, log-rank test). A total of 19 of 30 patients without MPR in their resected tumor following neoadjuvant chemotherapy died with a median OS time of 3 years, while only 2 of 7 patients with MPR died at 3.1 and 5 years, respectively (Figure 3D, P=0.04, log-rank test).

Comment

Here, we demonstrated that induction cisplatin and docetaxel chemotherapy is feasible and associated with tolerable toxicity. Following surgery, though, only 57% of patients (21/37 surgically treated patients) initiated adjuvant erlotinib, and only 57% of these completed the planned 1 year of treatment, illustrating the difficulties of delivering prolonged adjuvant therapy. The MPR to induction chemotherapy was 19%, and MPR was predictive of OS on exploratory analysis.

Since adjuvant platinum-based chemotherapy became a standard treatment for patients with resected, high-risk NSCLCs,(1–3) a common pathway for investigating novel agents in this setting has followed the paradigm of selecting drugs with activity in advanced disease, and incorporating them into standard-of-care adjuvant therapy. (*e.g.*, gefitinib,(17) erlotinib,(18) bevacizumab(19)). Our study attempted to evaluate, among other endpoints, the role of erlotinib given for 12 months after surgery. Despite completing accrual in 2.3 years, the final trial analysis was only conducted 5 years after the last patient underwent surgery, when 45% of the death events had occurred and DFS and OS could be reported with a high degree of confidence, and neither showed significant improvements compared to historical controls. When adjuvant therapy is utilized, recurrence or death are the only efficacy endpoints that can be evaluated and necessitate a long follow up time for accurate readout. Moreover, the heterogeneity of the trial population as regards to completing induction therapy, surgery, adjuvant radiation therapy and erlotinib further limit interpretations of the impact of each treatment component on clinical outcomes. With the current diversity and speed of development of novel agents for metastatic NSCLC, a thorough evaluation of promising drugs in early stage disease setting becomes impossible, especially if even small scale studies take a long time to mature.

Since conception of this trial, knowledge has evolved on the role of EGFR inhibitors in NSCLC, rendering some of the hypothesis to be tested in this trial obsolete. In metastatic disease, erlotinib use is now restricted to patients that harbor an activating tumor *EGFR* mutation.(20) Because molecular profiling of patients with non-metastatic NSCLC was not standard practice in our center when this study was conducted, we do not have data on the distribution of patients according to *EGFR* mutation. After this study finished accrual, results of a randomized phase 3 trial evaluating adjuvant erlotinib in patients with resected NSCLC selected based on EGFR overexpression or amplification became available, and did not demonstrate any benefit from EGFR inhibitor use in the trial population overall (RADIANT trial).(18) The fact that in our study, patients that initiated erlotinib had a better DFS does not necessarily imply that the drug improved outcomes, as a selection bias was very likely. In RADIANT, there was a signal of improved RFS in patients with an *EGFR* mutation. (18) Only 59% of the patients in RADIANT completed the planned 2 years of adjuvant erlotinib, which is consistent with our findings, and demonstrate that even targeted agents with a perceived favorable toxicity profile may not be feasible for long-term adjuvant use. A series of randomized trials (ALCHEMIST) evaluating adjuvant erlotinib within the subset of *EGFR* mutant patients is ongoing (NCT02193282). Given that these trials investigate agents in the adjuvant setting, concerns remain regarding the feasibility of completing accrual expeditiously, compliance with long-term drug use, and possibility of generating efficacy signals in a timely manner that could inform standard-of-care treatment for this patient population.

In contrast to some of the limitations of adjuvant therapy clinical trial designs, the current study provides a path forward towards relying on induction therapy to find efficacy signals in smaller-scale trials. We demonstrated that cisplatin and docetaxel led to a PR by RECIST in 60% of patients, mediastinal downstaging in 33% of patients, and MPR in 19% of patients. In an exploratory analysis, a CR in the nodes and/or a MPR in the primary tumor were associated with improved OS (Figure 3 B, C, D), in line with previous reports.(21) In

our study, imaging response by RECIST was not associated with better long-term outcomes, corroborating previous findings demonstrating a poor correlation between response by imaging and histopathological criteria, and OS.(22) However, MPR differentiated between long-term favorable and unfavorable outcomes (as did nodal CR), and has the advantage of being applicable to both node positive and negative patients on initial staging. Recently, Hellmann et al. (21) reviewed the results clinical studies that used MPR as a surrogate of efficacy provided by neoadjuvant chemotherapy in patients with resectable NSCLC. Our retrospective analysis of 192 patients with resected NSCLCs treated with neoadjuvant chemotherapy showed a MPR rate of 19% and a significant correlation between the degree of pathological response and OS and DFS of patients treated with neoadjuvant chemotherapy compared with historical controls (13). Other groups (14, 23) reported a MPR rate of 22% of patients with stage I–IIIA NSCLCs who received induction chemotherapy. Hellmann et al. propose incorporating MPR as a surrogate of survival benefit in future trials of neoadjuvant therapies for early stage NSCLC. Building on these results, the MD Anderson Thoracic Oncology Program has selected cisplatin and docetaxel as the backbone induction regimen for future studies, and defined MPR as the primary endpoint for subsequent phase II trials,(21). A series of phase II trials adding novel agents to the cisplatin and docetaxel induction regimen could provide short-term information regarding potential improvements in MPR rate. This platform of studies could screen a higher number of compounds in a shorter period of time, given the almost immediate read out of the primary outcome. Such program could triage drugs that would merit further evaluation in larger studies aimed at demonstrating if the short-term improvements in MPR would translate into long-term improvements in survival. Using this design, we have launched a phase I/II study evaluating cisplatin, docetaxel and nintedanib prior to surgery (NCT02225405), and a phase 2 study of nivolumab versus ipilimumab/nivolumab prior to surgery, both utilizing MPR as primary endpoint.

In conclusion, this study demonstrated that induction cisplatin and docetaxel was feasible, and is a reasonable treatment option for patients with resectable NSCLC. There was limited value of adding erlotinib in the adjuvant setting in unselected patients. Given the positive associations of MPR with long-term survival in this and other studies,(13) we have adopted MPR as the primary endpoint for small-scale, signal finding studies to screen a larger number of compounds for activity in early stage/locally advanced disease, and improve selection of compounds that should be tested in later-phase trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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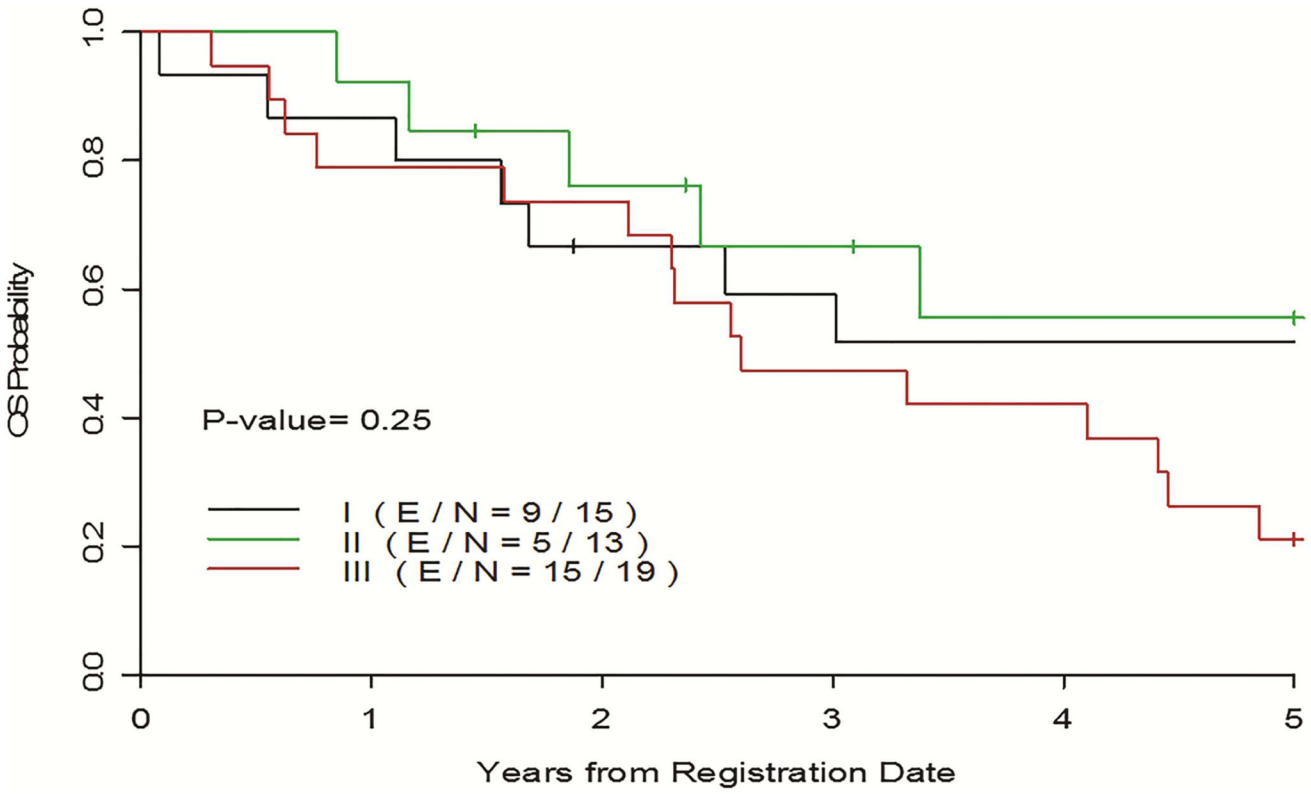

Figure 1.

Overall survival according to stage. Overall survival (OS) by stage in whole study population. E: number of events; N: number of patients.

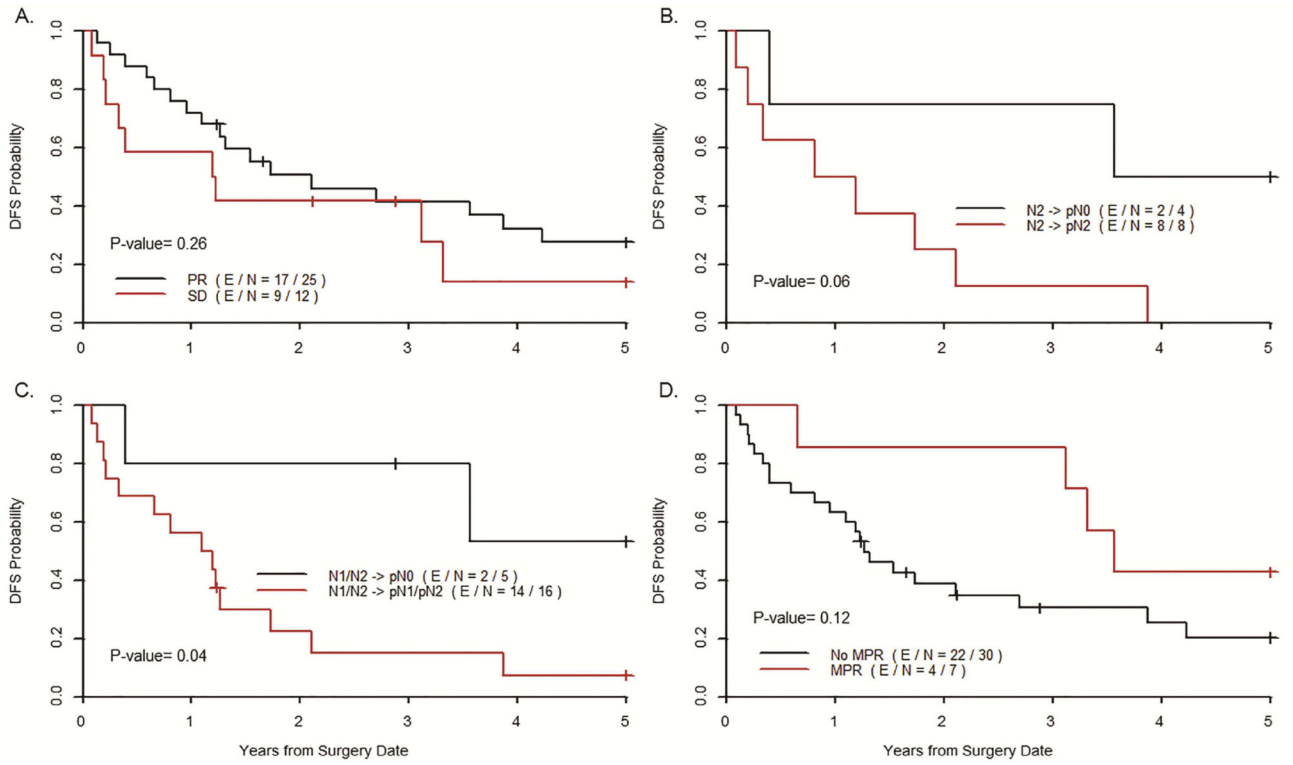

Figure 2.

Disease-free analysis in surgically resected patients. (*A–D)* Disease-free survival (DFS) according to response by imaging studies (A), mediastinal downstaging (B), pathologic complete mediastinal and nodal response (C), or major pathologic response (MPR) (D).

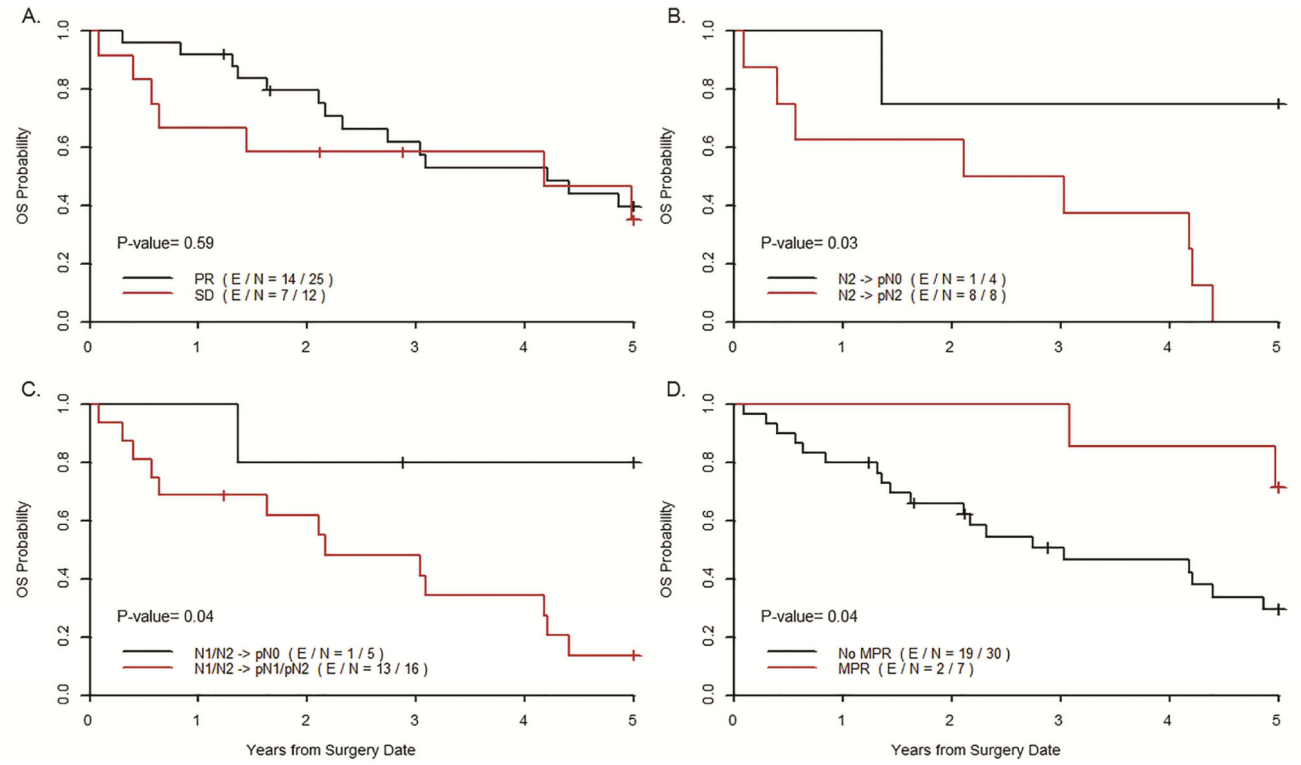

Figure 3.

Overall survival analysis in surgically resected patients. (*A–D*) OS according to response by imaging studies (A), mediastinal downstaging (B), pathologic complete mediastinal and nodal response (C), or MPR (D).

Table 1

Baseline characteristics of eligible patients

Characteristic	Number of patients (%) N=47
Median age, years (range)	64 (42–80)
Performance status	
0	13 (28%)
1	33 (70%)
2	1 (2%)
Sex	
Female	18 (38%)
Male	29 (62%)
Histology	
Non-small cell carcinoma, NOS	2 (4%)
Adenocarcinoma	22 (47%)
Squamous cell carcinoma	18 (38%)
Sarcomatoid carcinoma	4 (9%)
Adenosquamous cell carcinoma	1 (2%)
Pre-Treatment Stage	
IA	1 (2%)
IB (tumor size < 4 cm)	1 (2%)
IB (tumor size ≥ 4 cm)	13 (28%)
IIA	0 (0%)
IIB	13 (28%)
IIIA	18 (38%)
IIIB	1 (2%)
Smoking Status	
Never	7 (15%)
Former	8 (17%)
Current	32 (68%)

Table 2

Treatment characteristics

Parameter	
Number of patients initiating induction chemotherapy	47
Total number of induction chemotherapy cycles	131
Median number of induction chemotherapy cycles/patient (range)	3 (1 – 3)
Number of patients (%) with cisplatin dose reductions	
no dose reductions	41 (87%)
1 level	6 (13%)
2 levels	0
Number of patients (%) with docetaxel dose reductions	
no dose reductions	44 (94%)
1 level	3 (6%)
2 levels	0
Number of patients (%) with early induction treatment discontinuation due to:	
toxicities	6 (13%)
disease progression	0
refused	0
death	1 (2%)
Surgery, number of patients (%)	
no surgery	10 (21%)
segmentectomy / wedge resection	2 (4%)
lobectomy	31 (66%)
pneumonectomy	4 (9%)
Adjuvant radiation therapy, number of patients (%)	
no	39 (83%)
yes	8 (17%)
Adjuvant erlotinib, number of patients (%)	
initiated	21 (45%)
completed 12 months	12 (26%)
Median time on adjuvant erlotinib, months (range)	12 (0.03 –12)
Number of patients (%) with erlotinib dose reductions	
no dose reductions	16 (76%)
1 level	5 (24%)
2 levels	0
Number of patients (%) with early adjuvant erlotinib discontinuation due to:	
toxicities	6 (29%)

Parameter	
disease progression	3 (14%)

Table 3

Most common worst toxicities by grade (2–5) per patient during induction chemotherapy

	Number of Patients (%) N=47			
Grade	**2**	**3**	**4**	**5**
Hematologic toxicities				
Anemia	7 (15%)	3 (6%)		
Thrombocytopenia	1 (2%)			
Granulocytopenia		3 (6%)	9 (19%)	
Febrile granulocytopenia	1 (2%)	1 (2%)		
Non-hematologic toxicities				
Fatigue	3 (6%)	2 (4%)		
Alopecia	12 (25%)			
Hypoglycemia	2 (4%)	1 (2%)		
Hyperglycemia	2 (4%)	1 (2%)		
Dehydration	2 (4%)	1 (2%)		
Abdominal pain	2 (4%)	1 (2%)		
Elevated bilirubin	2 (4%)	1 (2%)		
Dysgeusia	2 (4%)			
Hypokalemia		3 (6%)	1 (2%)	
Hyponatremia		3 (6%)		
Infection (Normal ANC)		1 (2%)	2 (4%)	1 (2%)
Nausea/Vomit	4 (9%)	2 (4%)		

Table 4

Most common worst toxicities by grade (2–5) per patient during adjuvant erlotinib

	Number of Patients (%) N=21			
Grade	**2**	**3**	**4**	**5**
Non-hematologic toxicities				
Diarrhea	2 (10%)			
Skin rash	3 (14%)			