Original article

Annals of Oncology 15: 389–398, 2004
DOI: 10.1093/annonc/mdh099

Neoadjuvant concurrent radiochemotherapy in locally advanced (IIIA–IIIB) non-small-cell lung cancer: long-term results according to downstaging

L. Trodella[1]*, P. Granone[2], S. Valente[3], S. Margaritora[2], G. Macis[4], A. Cesario[2], R. M. D'Angelillo[1], V. Valentini[1], G. M. Corbo[3], V. Porziella[2], S. Ramella[1], G. Tonini[5], D. Galetta[2], M. Ciresa[1], B. Vincenzi[5] & N. Cellini[1]

Departments of [1]Radiation Oncology, [2]Thoracic Surgery, [3]Respiratory Physiology and [4]Radiology, Università Cattolica del S. Cuore; [5]Department of Medical Oncology, Libera Università Campus Bio-Medico, Rome, Italy

Received 24 March 2003; revised 1 August 2003; accepted 17 December 2003

Background: To report the efficacy of induction treatment (IT) protocol with concurrent radiochemotherapy in locally advanced non-small-cell lung cancer (NSCLC), and to analyze downstaging as a surrogate end point.

Patients and methods: Patients with histo- or cytologically confirmed stage IIIA or IIIB NSCLC were treated according to an IT protocol followed by surgery. Downstaging was assessed for all resected patients.

Results: In the period between February 1992 and July 2000, 92 patients were enrolled in the study (57 IIIA, 35 IIIB). Response was observed in 63 patients; 56 patients underwent radical resection. Patients downstaged to stage 0–I (DS 0–I) showed a statistically significant improved disease-free survival (26.2 months pStage 0–I versus 11.2 months pStage II–III; $P = 0.0116$) and overall survival (median 32.5 months pStage 0–I versus 18.3 months pStage II–III; $P = 0.025$). Patients with DS 0–I had a significantly lower probability ($P = 0.0353$) of developing distant metastases estimated in 0.2963 odds ratio.

Conclusion: Neoadjuvant radiochemotherapy is feasible with good pathological DS results. Pathological downstaging was confirmed to have high predictive value. Its use is suggested in the short-term evaluation of induction protocols efficacy in locally advanced NSCLC.

Key words: concurrent radiochemotherapy, downstaging, integrated therapies, neoadjuvant radiotherapy, non-small cell lung cancer, stage IIIA-IIIB

Introduction

Locally advanced non-small-cell lung cancer (NSCLC) still represents a therapeutic challenge and the state-of-the-art is far from reach. The chances of a cure offered by single therapeutic options (chemotherapy, radiotherapy, surgery) are extremely poor. This fact represented the rationale for the many attempts at improvement carried out in recent years within a multidisciplinary setting.

Today there are variations in standard of care for patients with locally advanced disease: surgery may remain the main option for selected N2 patients, while an induction treatment protocol may be applied for marginally resectable disease [1]. Chemoradiation is offered for patients ineligible for surgery who can tolerate it [2]. Recent data show that survival in locally advanced NSCLC is improved by the addition of chemotherapy to radiotherapy and/or surgery [3–6].

Several studies have explored the use of induction therapy (IT) followed by surgical resection [6–11]. These studies have shown good results in terms of survival provided that radical surgical resection could be feasible, morbidity rate being in the range 30–38.5% [6, 12–14] and mortality 2.5–8% [6, 10, 15]. Initially criticized because of the presumed higher incidence of post-operative morbidity and mortality, IT protocols based on the concurrent administration of chemoradiation are now applied.

There are no well-established criteria to assess the value of an IT protocol (overall efficacy), because overall 5-year survival has proved to be an impractical end point. This is due the high mortality rate in the first 3 years. For these reasons some authors have used surrogate end points such as shorter-term overall survival (3 years) [16] for the evaluation of an IT protocol efficacy. Several studies have explored some surrogate end points such as tumor regression [17–19] or nodal clearance [20] as short-term predictors of long-term survival.

We report herein our experience with concurrent radiochemotherapy in locally advanced clinical stage IIIA and IIIB NSCLC. Downstaging was assessed *per se* in order to analyze it as a surrogate end point in the evaluation of efficacy of an IT protocol and

Correspondence to: Dr L. Trodella, Department of Radiation Oncology, 'Università Cattolica del Sacro Cuore', Largo A. Gemelli 8, 00168 Rome, Italy. Tel: +39-630-155-226; E-mail: ltrodella@rm.unicatt.it

its possible predictive value in terms of overall long-term survival. Furthermore we here explored the impact of this parameter in order to evaluate the effect of local control on survival.

Patients and methods

Patient selection

Patients older than 18 years with histologically or cytologically confirmed NSCLC, clinical stage IIIA or IIIB, performance status [according to the Eastern Cooperative Oncology Group (ECOG)] 0–1, who had not undergone any previous oncologic treatment, were enrolled in this trial of combined neoadjuvant chemoradiation. No comorbidities contra-indicating concurrent chemoradiation and/or surgery were present. The goal was for patients to re-enter surgical resectability, so we have enrolled patients with stage IIIA (generally considered as marginally resectable) and IIIB–T4 (unresectable, where surgery can be considered if downstaging is achieved by any procedure). Selection of IIIB–N3 patients was strict. In particular, the N3 parameter included only one node proven to be involved by mediastinoscopy, with a maximum diameter of 1 cm, so as to be considered potentially curable with concurrent radiochemotherapy. The whole trial, including two different chemotherapy regimens, can be considered as a phase II study because the core is represented by the homogeneous radiation treatment. In this setting it should be stressed that chemotherapy has been focused as a radiotherapy 'enhancer'. Patients with malignant pleural effusion and/or positive supraclavicular adenopathy were excluded from the study.

Generic eligibility criteria for oncologic treatment, including adequate blood chemistry, hepatic and renal function, no pulmonary or cardiovascular contraindications and life expectancy longer than 6 months were applied. Informed consent was obtained from all patients prior to the start of induction protocol.

Assessment procedure

Pre-treatment evaluation included patient history, physical examination, performance status, standard chest X-ray, complete blood chemistry, tumor markers, CT of the chest, brain and upper abdomen, whole-body radionuclide scan, fiberoptic bronchoscopy. Standard X-ray and CT were performed to rule out suspicion of bone metastasis. Upon suspect CT, mediastinal involvement has always been confirmed cyto- or histologically, by mediastinoscopy. In addition to the staging procedure, cardiopulmonary and lung function tests, electrocardiogram and echocardiogram were performed to assess the general status of each patient.

CEA, TPA, NSE, CYFRA 21.1 and LDH have been investigated at diagnosis and during follow-up (except CYFRA which was routinely introduced in our center in 1999), but data are incomplete and no analysis has been performed. During treatment, complete blood count and clinical examination were carried out every week; furthermore, blood chemistry was repeated before every chemotherapeutic cycle; a control chest X-ray was performed when the dose of 20–25 Gy had been reached. A complete clinical and radiological re-evaluation was performed 4 weeks after the end of treatment.

Before treatment and after restaging procedures, all patients were carefully evaluated by an interdisciplinary team composed of a pneumologist, a thoracic surgeon, a medical and radiation oncologist and a radiologist. The clinical response to IT was assessed according to the World Health Organization (WHO) criteria. The sum of the complete response rate plus the partial response rate was defined as major clinical response.

Treatment design

The treatment plan is illustrated in Figure 1. Radiotherapy was administered with an angled field technique to include in the isodose 100% (± 5%) area all the target volume, with a maximum dose to the spinal cord of 36 Gy. The median International Commission on Radiation Units and Measurements (ICRU) total referred dose was 50.4 Gy with classical (1.8 Gy/day) or hyper (1.2 Gy/b.i.d.) fractionation. The planned target volume (PTV) consisted of primary tumor, nodal metastasis and first uninvolved nodal chain with 1.5 cm margin. Elective nodal irradiation was not administered. The treatment was CT planned with lung parenchyma correctional factors, and a linear photon accelerator (nominal energy 6–10 MV) was used in all cases. Advanced 2D technique was used for treatment planning. All patients were immobilized by customized devices.

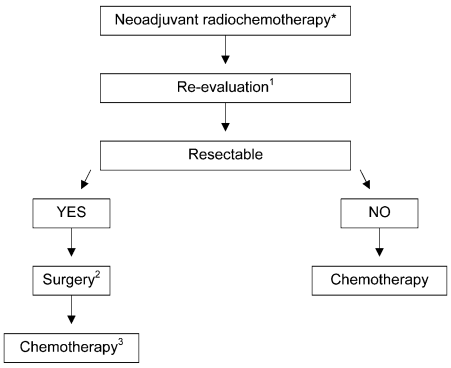

Figure 1. Treatment plan. *Chemotherapy regimens: carboplatin (CBDCA) 70 mg/mq/day in continuous venous infusion, during days 1–4 the first and last week of treatment (57 patients); cisplatin (CDDP) 20 mg/mq/day/bolus plus 5-FU 1 g/mq/day in continuous venous infusion, during days 1–4 of the first and last week of treatment (35 patients). [1]From 20 to a maximum of 30 days after the end of induction therapy. [2]Seven to 15 days after re-evaluation. [3]One month after surgery, if feasible.

Two different chemotherapy regimens were used: carboplatin (CBDCA) 70 mg/mq/day in continuous venous infusion, during days 1–4 of the first and last week of treatment (1992–1997) (scheme 1; CBCDART); cisplatin (CDDP) 20 mg/mq/day/bolus plus 5-FU 1 g/mq/day in continuous venous infusion, during days 1–4 of the first and last week of treatment (1998–2000) (scheme 2; FUPLART).

From 1992 to 2000 we have observed an improvement in delivering radiotherapy due to a better definition of target volume and the development of conformal therapy. Pneumonectomy rate decreased, testifying a valid 'organ sparing' effect. The switch in chemotherapy regimen was based on the good tolerability of the original scheme (CBCDA) and the better enhancement ratio with CDDP–5-FU with a likely better systemic control (spatial co-operation).

If necessary, antiemetics, antibiotics, sedatives, steroids, hematopoietic growth factors and gastric protectors were administered. When grade 2–3 esophageal, pulmonary and cardiac toxicity or grade 3–4 hematological and skin toxicity (RTOG scale [21]) appeared, treatment was temporarily interrupted, pending resolution. No change in the total dose of chemoradiation was adopted for grade 2 non-hematological toxicity or grade 3 hematological toxicity. A 25% dose reduction in chemotherapy was applied in case of grade 3 non-hematological toxicity or grade 4 hematological toxicity. Radiotherapy was discontinued in case of grade 4 non-hematological toxicity or persistent side effects (>14 days). Systemic chemotherapy was planned for all patients 1 month after surgical resection and for those judged inoperable. In every case three cycles of a two-drug chemotherapy with cisplatin was planned (with etoposide or vinorelbine); the exclusion criteria were a post-operative ECOG performance status ≥2 or patient's refusal.

Statistical analysis

The disease-free survival (DFS; time to local plus distant event) 'time to event' curve has been calculated with the Kaplan–Meier method [22] and statistical

Table 1. Characteristics of population

	All patients	CBCDART	FUPLART
No. of patients	92	68 (73.9%)	24 (26.1%)
Age (years)			
Median	62	64	62.5
Range	26–79	30–79	26–74
Sex			
Male	83 (90.2%)	62 (91.2%)	21 (87.5%)
Female	9 (9.8%)	6 (8.8%)	3 (12.5%)
ECOG performance status			
0	77 (83.7%)	54 (79.4%)	23 (95.8%)
1	15 (16.3%)	14 (20.6%)	1 (4.2%)
Histological cell type			
Squamous cell	45 (48.9%)	35 (51.5%)	10 (41.6%)
Adenocarcinoma	33 (35.8%)	24 (35.3%)	9 (37.5%)
Large cell	13 (14.1%)	8 (11.7%)	5 (20.8%)
Adenosquamous	1 (1.2%)	1 (1.5%)	0 (0%)
Stage IIIA	57 (61.9%)	41 (60.3%)	16 (66.6%)
T1–3 N2	46 (80.7%)	33 (80.5%)	13 (81.2%)
T3 N1	11 (19.3%)	8 (19.5%)	3 (18.8%)
Stage IIIB	35 (38.1%)	27 (39.7%)	8 (33.4%)
T4 N0–2	30 (85.7%)	23 (85.1%)	7 (87.5%)
T1–3 N3	4 (11.5%)	4 (14.9%)	0 (0%)
T4 N3	1 (2.8%)	0 (0%)	1 (12.5%)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Acute toxicity

Acute toxicity	All patients (total: 92)	CBCDART (total: 68)	FUPLART (total: 24)
Hematological			
Grade 1–2	35 (38%)	27 (39.7%)	8 (33%)
Grade 3–4	5 (5.5%)	5 (7.3%)	–
Non-hematological			
Esophagus			
Grade 1–2	11 (11.9%)	5 (7.3%)	6 (25%)
Grade 3–4	1 (1.1%)	–	1 (1.4%)
Lung			
Grade 1–2	–	–	–
Grade 3–4	1 (1.1%)	–1 (4%)	

Table 3. Clinical response rate

	All patients (total: 91)	CBCDA group (total: 67)	FUPLART group (total: 24)
PR + CR	63 (69.2%)	45 (67.2%)	18 (75%)
NC	22 (24.2%)	19 (28.3%)	3 (12.5%)
PD	6 (6.6%)	3 (4.5%)	3 (12.5%)

CR, complete response; NC, no change; PD, progressive disease; PR, partial response.

significance of the difference has been assessed with the log-rank test [23, 24]. A similar procedure was carried out to compare the 'time to event' survival curves. Hazard ratio with 95% confidence interval was calculated as well for DFS and overall survival (OS). Differences between groups were compared adopting the Fisher exact test [25]; the relative risk (RR) with 95% confidence interval (CI) has been calculated with the Woolf approximation.

Results

In the period between February 1992 and July 2000, 92 patients with histo- or cytologically confirmed locally advanced NSCLC were enrolled in this phase II trial of concurrent neoadjuvant chemoradiation. Patients' characteristics are reported in Table 1. Seventy-seven of 92 (83.7%) patients had a performance status of 0 (according to the ECOG scale); five patients were IIIB–N3. Among the 92 patients, 68 were treated with scheme 1 (CBDCA + RT) and 24 with scheme 2 (CDDP and 5-FU + hyperfractionated RT). At the time of this evaluation the mean follow-up was 25.3 months with the last patient enrolled 21 months previously. Forty-six of 57 (80.7%) IIIA patients were clinical N2; 30 of 35 (85.7%) IIIB patients were T4 N0–2.

Induction therapy (IT)

Ninety-one of 92 (98.9%) patients received the treatment as planned and are evaluable for response. One patient discontinued treatment due to a decline in performance status. Acute toxicity [according to the Radiation Therapy Oncology Group (RTOG) scale] is summarized in Table 2: grade 3–4 hematological toxicity was observed in five patients, all in the CBCDA group; grade 1–2 esophageal toxicity was present in 11.9% of patients. Two patients had grade 3–4 non-hematological toxicity: one pulmonary and one esophageal both in the FUPLART scheme. In 12 of 92 (13%) patients, treatment was interrupted due to toxicity, for a mean period of 5 days (range 2–12 days).

Upon restaging a major clinical response was observed in 63 of 91 patients (69.2%). Twenty-two of 91 patients (24.2%) showed stable disease and six of 91 patients (6.6%) developed systemic progressive disease (PD). No local PD was observed. The response rate according to adopted chemotherapy regimens is reported in Table 3.

Surgery

Based on restaging, 61 of 91 patients (67%), 43 in the CBCDART group and 18 in the FUPLART group, were judged to be resectable and operated upon. Fifty-six of 91 (61.5%) patients were completely resected; 41 patients in the CBCDART group and 15 in the FUPLART group, including complete mediastinal lymph node dissection (CMLND). Resectability rate was 91.8%. In three patients CMLND was not performed and thus they were included in the Nx status group (downstaging unknown). Two patients

Table 4. Downstaging according to clinical and pathological staging

Clinical staging (no. of patients)	Pathological staging			
	IIIA	II	I	0
IIIA (36)	12	10	5	9
IIIB (20)	2	6	5	7
Total (56)	14 (25%)	16 (28.6%)	10 (17.8%)	16 (28.6%)

Table 5. Downstaging according to clinical and pathological T-status

Clinical T-status (no. of patients)	Pathological downstaging			
	T3	T2	T1	T0
T4 (18)	2	4	2	10
T3 (26)	8	4	4	10
T2 (10)	–	4	5	1
T1 (2)	–	–	1	1
Total (56)	10 (17.8%)	12 (21.4%)	12 (21.4%)	22 (39.4%)

could not be resected due to macroscopic residual invasion of intrathoracic extra-pulmonary organs. Regarding the type of surgery, all operations were performed by the same surgical team; there were 28 lobectomies, nine bilobectomies and 19 pneumonectomies. As previously stated, in recent years we have recorded a decreasing number of pneumonectomies: 1992–1995, 11 of 24 (45.8%); 1996–2000, eight of 32 (25%).

Clinical staging of the 19 pneumonectomized patients was as follows: 10 IIIB–T4, nine IIIA–N2 (including four T3 patients). Three patients with clinical N3 disease (confirmed at mediastinoscopy) did not show any residual disease at CT re-evaluation. Redo mediastinoscopy was carried out and biopsies were taken in the same area of the first procedure. Upon frozen section confirmation of tumor absence, the operation proceeded with thoracotomy.

Mortality

The perioperative mortality rate (within 30 days) was 11.4% (seven of 61). Five of seven patients were treated with pneumonectomy, one with bilobectomy and one with lobectomy. Causes of death were a cardiovascular disease in four patients, massive postoperative bleeding in one, respiratory failure in one and pleural empyema and septicemia in one due to persistent broncho-pleural fistula; six of seven patients were in the CBCDART group (six of 43; 13.9%), one in the FUPLART group (one of 18; 5.5%).

Morbidity

The major morbidity rate was 14.7% (nine of 61 patients); it included one pulmonary abscess, one acute hemorrhage (re-thoracotomy), one pleural empyema, one bronchopleural fistula, two myocardial infarctions, two pulmonary failures and one pulmonary embolism plus pneumonia. Three of these patients received pneumonectomy and three bilobectomy; in the remaining three patients lobectomy, lobectomy plus wall resection and thoracotomy were performed. Of these nine patients, nine of 43 (16.2%) were treated with CBCDART, two of 18 (11.1%) with FUPLART.

Definitive histological assessment and pathological downstaging

The overall downstaging rate was 75% (Table 4). Sixteen of 56 (28.6%) patients were downstaged to stage 0, 10 of 56 to stage I (17.8%), 16 of 56 (28.6%) to stage II. Stage III persisted in 14 of 56 (25%) patients. In Tables 5 and 6 clinical T and N are compared with pathological stages.

According to the different induction schemes adopted, we observed 15 of 41 (36.6%) patients downstaged to stage 0–I in the CBCDART arm, and 11 of 15 (73.3%) in the FUPLART group (Table 7).

Patterns of failure after surgery

Four patients had local recurrence on the bronchial stump. Twenty-three patients had distant recurrence (19 had been treated with adjuvant chemotherapy) and five had local and distant recurrence. Of the nine patients with local recurrence seven had had R1 resection and in one case cancer was close to the resection margins (<5 mm).

Seven of 56 (12.5%) patients had brain metastasis as first and single site of recurrence: three were classified at pathological restaging as stage II–III, and four as stage 0–I; five patients had adenocarcinoma and two squamous cell carcinoma: five were classified at diagnosis as IIIA, two as IIIB (one T4N2 and one T2N3).

Table 6. Downstaging according to clinical and pathological N-status

Clinical N-status (no. of patients)	Pathological downstaging		
	N2	N1	N0
N3 (3)	1	–	2
N2 (42)	11	9	22
N1 (9)	1	1	7
N0 (2)	–	–	2
Total (56)	13 (23.3%)	10 (17.8%)	33 (58.9%)

Table 7. Downstaging according to different adopted scheme

Scheme (no. of resected patients)	Pathological downstaging			
	IIIA	II	I	0
CBCDART (41)	13	13	8	7
FUPLART (15)	1	3	2	9
Total (56)	14 (25%)	16 (28.6%)	10 (17.8%)	16 (28.6%)

Table 8. Overall survival

	Median survival	Overall survival (%)				
		1 year	2 years	3 years	4 years	5 years
All patients	17.2 months	59	37	19	17	15
Operated	23.3 months	72	48	27	25	23
pStage 0–I	32.5 months	77	65	49	43	37
pStage II–III	18.3 months	66	8	17	14	10

Adjuvant chemotherapy

Among the 56 patients who underwent radical resection, in 36 patients adjuvant chemotherapy was started; 28 received three to six cycles. In eight patients treatment was stopped early due to hematological toxicity in four patients, one for deep venous thrombosis, one for early brain recurrence (3 months after re-evaluation), one for decline in performance status and one due to a delayed bronchial fistula (80 days after surgery).

The causes of the 20 withdrawals from adjuvant treatment were seven post-operative deaths, four because of patient's refusal, three for PS >2, one for pulmonary insufficiency after surgery, one for onset of new cancer (colon), one for patient's oncologist refusal, and one patient was lost after surgery.

Survival

Overall survival (OS) for all study patients was 19% at 3 years and 15% at 5 years (Table 8 and Figure 2). Significant differences were found when the so-called 'responders', who underwent radical resection, were compared with patients who did not undergo surgery (median survival was 25.4 months in the operated versus

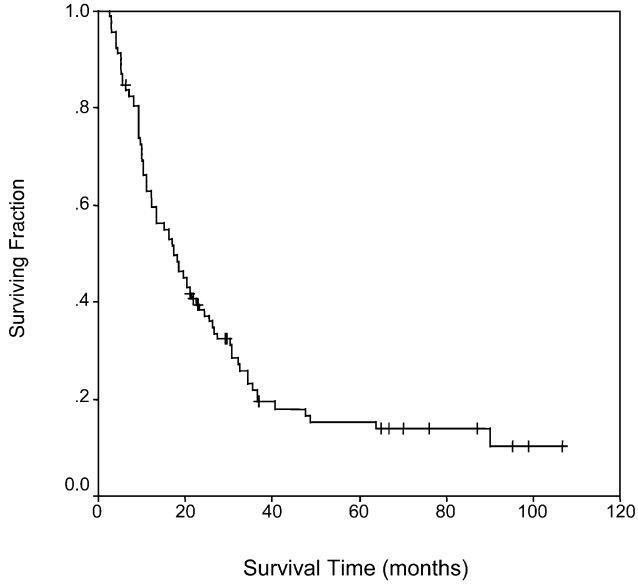

Figure 2. Overall survival of the entire group.

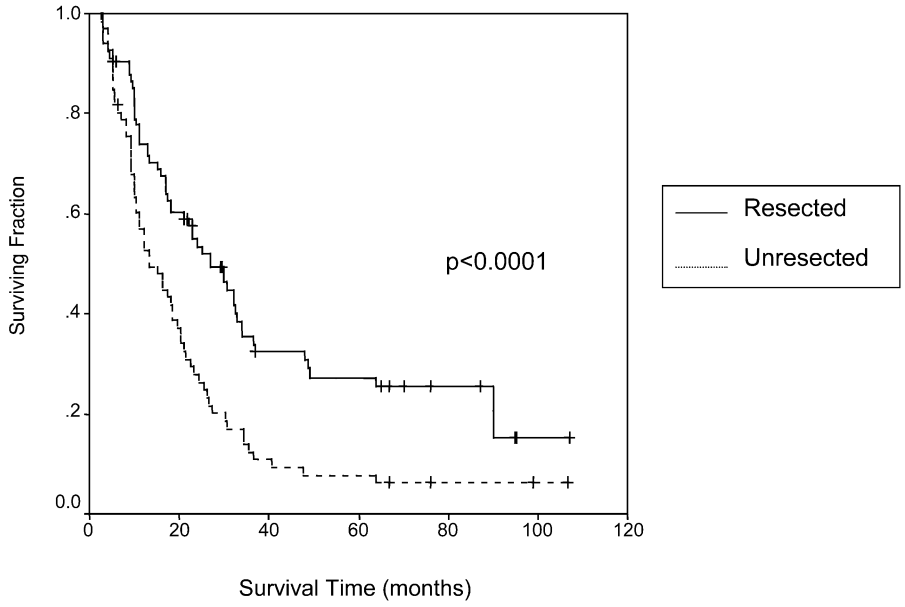

Figure 3. Overall survival for resected and unresected patients.

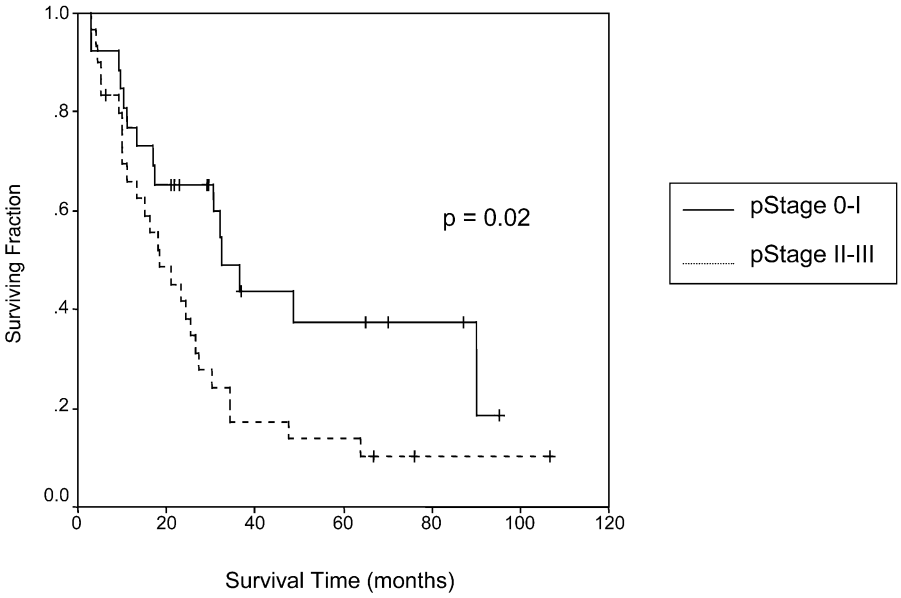

Figure 4. Overall survival according to pathological downstaging.

10.2 months in the not operated patients; P <0.0001; Figure 3). Five patients who underwent surgery, but without radical interventions, had a median survival of 14.2 months.

Downstaging

The best results in survival rate were achieved in those patients in whom a pathological downstaging to stage 0–I had been obtained (median survival 32.5 months pStage 0–I versus 18.3 months pStage II–III, P = 0.025; Figure 4). In patients with pathological downstaging to stage 0–I (DS 0–I), with no nodal involvement, a median survival of 32.5 months had been obtained. Three- and 5-year survival rates of 49% and 37% were observed. Disease-free survival (DFS) is described in Table 9. A better median DFS was achieved in pStage 0–I (26.2 months) than in pStage II–III (11.2 months; P = 0.0116; HR 2.099, 95% CI 1.194–4.084; Figure 5).

In patients downstaged to 0–I a distant failure was experienced in eight of 26 (30.7%; four patients were treated with adjuvant chemotherapy). On the other hand, patients downstaged to stage II–III showed a 60% (18 of 30) distant failure rate (15 patients

Table 9. Disease-free survival

	Median	Disease-free survival (%)				
		1 year	2 years	3 years	4 years	5 years
Resected	12.9 months	51	30	21	18	18
pStage 0–I	26.2 months	61	53	37	31	31
pStage II–III	11.2 months	41	10	7	7	7

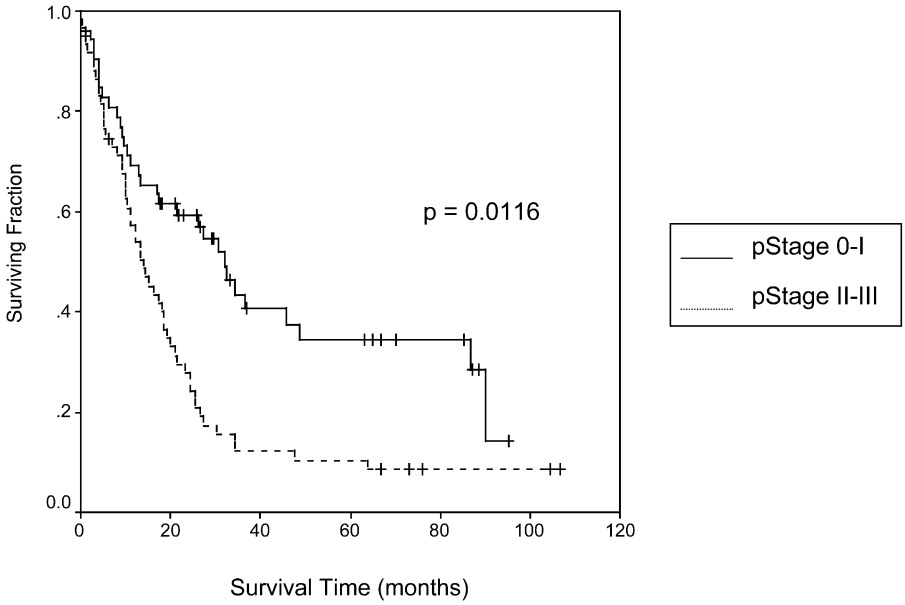

Figure 5. Disease-free survival according to pathological downstaging.

were treated with adjuvant chemotherapy). According to these results patients with DS 0–I had a significant lower probability ($P = 0.0353$) of developing distant metastasis estimated in an odds ratio of: 0.2963 (95% CI 0.09784–0.8973). Adjuvant chemotherapy did not influence the systemic spread (odds ratio 2.076; 95% CI 0.6716–6.415; $P = 0.2669$).

Discussion

Approximately one-third of patients with NSCLC are clinical stage III: of these 32% are lost for distant metastasis and one-third due to absence of local control [26]. At present the combination of chemoradiotherapy (sequential, concurrent, mixed) has been widely explored. The concurrent scheme is generally considered the standard option for patients not eligible for surgery with locally advanced disease [2]. Absence of local control is a major obstacle to long-term cure in patients with locally advanced NSCLC, as the 2-year in-field progression rate ranges from 26% to 45% after curative chemoradiotherapy [27, 28]. Radical surgery still remains the best chance of obtaining local control and the only modality which may cure patients.

When surgery is not reasonably feasible, any therapy that by downstaging the tumor makes the patient re-enter resectability criteria has a direct impact on the local control rate and thus on the general outcome. To date, discussion is focused on two major problems: which is the best multi-modality approach, and is there an end point different from overall long-term survival for the evaluation of the effectiveness of an induction protocol? Regarding the first question, the most popular scheme is to perform chemo or radiochemo induction protocol as neoadjuvant to surgery.

The studies so far have addressed and explored the feasibility and efficacy of multi-modality neoadjuvant treatments and yet an extreme lack of homogeneity is present regarding the kind of chemotherapeutic agent or agents used, concomitant or sequential radiotherapy and its characteristics (energy source, technique, fractionation, total dose, irradiated volume). For these reasons definitive conclusions cannot be drawn to assess which is to date the best induction treatment.

In our opinion a general beneficial effect in terms of efficacy may be identified when a multimodality approach is used combining neoadjuvant irradiation and chemotherapy, which we here demonstrated to be feasible [29] with limited volume and low total dose. Table 10 shows the published trial where trimodality treatment was explored.

Table 10. clinical trial exploring neoadjuvant radiochemotherapy

Author	No. of patients	Stage	No. of radical resections	Pathological CR
SWOG [6]	126	IIIAN2–IIIB	89 (70.6%)	19 (21.3%)
ESSEN [8]	94	IIIA–IIIB	60 (63.8%)	24 (40%)
Faber et al. [30]	85	III	60 (70.6%)	17 (28.3%)
Weiden and Piantadosi [31]	85	III	44 (51.7%)	8 (18.2%)
Strauss et al. [42]	41	IIIA	31 (75.6%)	7 (22.5%)
Milstein et al. [7]	36	IIIA–B	20 (55.5%)	3 (15%)
Present study	92	IIIA–IIIB	56 (60.8%)	16 (28.5%)

CR, complete response.

The two largest phase II trials that explored the trimodality treatment are the SWOG [6] and ESSEN [8] trials. In the SWOG trial [6] 126 patients were enrolled and treated with a total dose of radiotherapy of 45 Gy, administered in 25 daily, 1.8 Gy fractions over 5 weeks, and concurrent cisplatin (CDDP) 50 mg/m^2 on days 1, 8, 29 and 36 plus etoposide (VP-16) 50 mg/m^2 on days 1–5 and 29–33. After concurrent chemoradiotherapy 101 patients (80.1%) underwent surgery, 89 of 101 (88%) had a complete resection; the perioperative mortality rate was 12.8% (13 of 101). In 19 of 89 patients (21.3%) no tumor was found in the pathological specimens.

In the ESSEN trial [8] patients were treated with a mixed approach, which includes three cycles of induction chemotherapy with CDDP 60 mg/m^2 on days 1 and 7 (or 8) and VP-16 150 mg/m^2 on days 3, 4 and 5 repeated every 22 days, and one cycle concurrent with radiotherapy of CDDP 50 mg/m^2 on days 1 and 7 (or 8) and VP-16 100 mg/m^2 on days 3, 4 and 5. Hyperfractionated radiotherapy was adopted with 1.5 Gy b.i.d. for a total dose of 45 Gy. Seventy-five of 94 enrolled patients (79.7%) were considered eligible for surgery after IT protocol; 60 of 75 (80%) underwent radical surgery. The mortality rate was 5.3% (four of 75) with a 40% (24 of 60) pathological complete response.

In our study, 61 of 91 evaluable patients (67%) were eligible for surgery, and 56 of 61 (91.8%) underwent radical resection. In this series we observed a better survival for patients downstaged to pathological stage 0–I, with a median survival of 32.5 months and a 3-year survival of 49%. The results of DFS are interesting with a median value of 26.2 months and of 37% at 3 years. These results are similar to those reported by the SWOG and ESSEN trials, where radically resected patients with N0 disease had a 3-year survival of 44% and 38%, respectively.

We report a mortality rate of 11.4% (seven of 61), similar to that of the SWOG trial. An important factor to be underlined is that five of seven patients received pneumonectomy: we share Martin et al.'s hypothesis [14] that pneumonectomy is the major risk factor of mortality ratter than the type of induction therapy protocol adopted. As for the morbidity rate, Faber et al. [30] and Weiden and Piantadosi [31] reported a major morbidity rate of 22.5% (14 of 62 patients who underwent surgery) and 25.9% (14 of 54), respectively, while we reported a rate of 14.7% (nine of 61).

From the beginning of this trial we have adopted a radiotherapy approach with a low total dose and limited irradiated volume (only primary tumor with macroscopically involved lymph nodes) without elective nodal irradiation (ENI), because our goal was the re-enter resectability. This approch explains the low acute and late non-hematological toxicity as well as the morbidity rate. We believe that these two issues with conformal 3D radiotherapy technique could modify the morbidity rate after neoadjuvant concurrent chemoradiation.

The role of surgery was recently evidenced by the early results of the Intergroup Trial 0139 [32], where definitive chemoradiation was compared to a neoadjuvant chemoradiation in IIIAN2 (at proven mediastinoscopy) stage. In the ongoing analysis of the trial a significantly longer progression-free survival has been observed in patients who received surgery after neoadjuvant concurrent chemoradiation (14 versus 11.7 months; $P = 0.002$). A better overall 3-year survival (38% versus 33%) was also observed, but these data are not yet mature enough to determine a statistically significant difference.

The Paris trial [33] explored the trimodality treatment approach in IIIB patients. Eligibility criteria included a potentially resectable disease, defined as T4 disease with the involvement of the intrapericardial pulmonary artery, trachea, carina, left atrium or superior vena cava, and N3 patients. Induction treatment included a three-drug chemotherapy with 5-FU 1 g/m^2 from days 1 to 3 and days 31–33, CDDP 100 mg/m^2 on days 1 and 31 and vinblastine 4 mg/m^2 on days 1 and 31. Concurrent radiotherapy was applied with a split course of 21 Gy delivered as 1.5 Gy per fraction b.i.d. from days 1 to 9; a rest of 10–15 days and other 21 Gy with the same fractionation beginning on day 21. If resectable and medically operable, surgery was performed with a midline sternolaparotomy, radical resection of tumor mass, extensive mediastinal lymph node dissection (bilateral for N3 disease) and preventive bronchial omentoplasty. Forty patients were enrolled (21 with T4 disease, 19 with N3); 29 underwent thoracotomy and 24 were radical resected; 18 pneumonectomies were performed. In spite of aggressive surgery the mortality rate was 7% with 24% morbidity rate. Survival was strictly associated with post induction nodal status (N0–1) and radical resection.

In our series, 35 patients with stage IIIB were enrolled: 30 patients with the same type of T4 disease and only five carefully

selected N3 patients who underwent lateral thoracotomy only with negative redone mediastinoscopy. We believe that for these patients, especially for those with T4 disease, a multimodality approach including surgery could be applied.

We have explored the opportunity to analyze downstaging *per se* as a surrogate end point for the evaluation of the efficacy of a neoadjuvant approach. There is some evidence of the impact of tumor downstaging on other types of neoplasm such as rectal [17, 18] or esophageal tumors [19], while in lung cancer lymph-node clearance [20] has already been documented. We have shown that downstaging to pStage 0–I was significantly correlated with better long-term survival if compared to pStage II–III. These results substantially confirmed the reports by Choi et al. [34] and Martin et al. [16]. As compared to Martin's experience, we explored the value of downstaging in a more homogeneous group of patients. In fact, we have evaluated patients with clinical stages IIIA and IIIB only.

In this trial we have investigated the correlation between pathological downstaging and survival and distant recurrence rate. We have found that downstaging is directly and significantly correlated with disease-free survival and distant recurrence rate. This underlines the impact of local control on metastasis and survival. The disease-free interval seems to be a more reliable parameter, when the efficacy of an IT protocol is explored. Moreover the DFS has presumably a significant impact on the quality of life of patients (no cancer, no treatment; no treatment, no side-effects). To our best knowledge, this kind of correlation has never been explored.

Downstaging based on only radiotherapy is poor [35], while neoadjuvant chemotherapy shows a pathological complete response that ranges from 0% reported by Roth et al. [11] and Sugarbaker et al. [9] to 16.7% in Martini et al. [10]. Also in these cases the pCR has been translated with best overall survival. The role of adjuvant chemotherapy is still controversial: in our experience, 28 of 56 radically resected patients completed planned chemotherapy, but no significant influence on systemic spread was recorded. This small evidence is similar to the ALPI [36] and ECOG trials [37], which showed no benefit from adjuvant chemotherapy, while recent results of the IALT trial [38] re-considered the role of adjuvant chemotherapy with a small benefit of 4% at 5 years.

In the series of Robnett et al. [39], crude and 2-year actuarial rates of brain metastases of 19 and 30% respectively were recorded. On multivariate analysis independent prognostic factors were stage (IIIB versus IIIA) and timing of chemoradiation (sequential versus concurrent). In our analysis, seven patients had a brain metastasis as first site of recurrence and this small number did not provide any information about the impact of histology, staging at diagnosis or downstaging on the potential impact of prophylactic cranial irradiation for such patients.

Finally, pathological downstaging rate could be a reasonable surrogate end point to compare different IT protocols. In our series we observed a better rate of downstaging in those patients who received hyperfractionated radiotherapy and CDDP + 5-FU chemotherapy, but no data are available in the literature concerning an improvement in pathological response using different radiotherapy fractionations. A possible explanation could be that chemotherapy, as radiosensitizer, might have a better enhancement ratio with twice daily radiotherapy. In order to improve the pathological downstage rate, we have already explored in a phase I trial the maximum tolerated dose of weekly gemcitabine and concurrent radiotherapy [40]. The feasibility and pathological response of this combination treatment [41] is under investigation in a phase II trial.

On the basis of the reported experiences we can conclude that: treatment of locally advanced NSCLC remains challenging and there is still room for investigation; concurrent neoadjuvant radiochemotherapy is feasible with limited volume and low total dose; downstaging to early stages (0–I) represents a direct indication of the effectiveness of any multimodality approach and is significantly correlated with disease-free interval and distant recurrence rate; the rate of downstaging seems better in neoadjuvant combined chemoradiation than chemotherapy and radiotherapy as only treatment; in this setting the main advantage of long-term outcome in planning an induction protocol in locally advanced NSCLC is the opportunity to obtain a significant pathological downstage rate.

References

1. http://www.nci.nih.gov/cancerinfo/pdq/treatment/non-small-cell-lung/healthprofessional
2. ASCO. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. J Clin Oncol 1997; 15: 2996–3018.
3. Dillman RO, Seagren SL, Propert KJ et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990; 323: 940–945.
4. Sause WT, Scott C, Taylor S et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst 1995; 87: 198–205.
5. Jeremic B, Shibamoto Y, Acimovic L et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. J Clin Oncol 1996; 14: 1065–1070.
6. Albain KS, Rusch VW, Crowley JJ et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol. 1995; 13: 1880–1892.
7. Milstein D, Kuten A, Saute M et al. Preoperative concurrent chemoradiotherapy for unresectable Stage III nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys 1996; 34: 1125–1132.
8. Eberhardt W, Wilke H, Stamatis G et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. J Clin Oncol 1998; 16: 622–634.
9. Sugarbaker DJ, Herndon J, Kohman LJ et al. Results of cancer and leukemia group B protocol 8935. A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. Cancer and Leukemia Group B Thoracic Surgery Group. J Thorac Cardiovasc Surg 1995; 109: 473–483.
10. Martini N, Kris MG, Flehinger BJ et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. Ann Thorac Surg 1993; 55: 1365–1373.

11. Roth JA, Fossella F, Komaki R et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994; 86: 673–680.
12. Deslauriers J, Ginsberg RJ, Piantadosi S et al. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. Chest 1994; 106: 329S–330S.
13. Duque JL, Ramos G, Castrodeza J et al. Early complications in surgical treatment of lung cancer: a prospective, multicenter study. Ann Thorac Surg 1997; 63: 944–950.
14. Martin J, Ginsberg RJ, Abolhoda A et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. Ann Thorac Surg 2001; 72: 1149–1154.
15. Pisters KM, Ginsberg RJ, Giroux DJ et al. Induction chemotherapy before surgery for early-stage lung cancer: a novel approach. J Thorac Cardiovasc Surg 2000; 119: 429–439.
16. Martin J, Ginsberg RJ, Venkatraman ES et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. J Clin Oncol 2002; 20: 1989–1995.
17. Valentini V, Coco C, Picciocchi A. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002; 53: 664–674.
18. Wheeler JM, Warren BF, Mortensen NJ et al. Quantification of histologic regression of rectal cancer after irradiation: a proposal for a modified staging system. Dis Colon Rectum 2002; 45: 1051–1056.
19. Mandard AM, Dalibard F, Mandard JC et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994; 73: 2680–2686.
20. Betticher DC, Hsu Schmitz SF, Totsch M et al. Mediastinal lymph node clearance after docetaxel–cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003; 21: 1752–1759.
21. Perez CA, Brady LW. Principles and Practice of Radiation Oncology. Philadelphia, PA: Lippincott 1992; 51–55.
22. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457–481.
23. Cox DR. Regression models and life-tables. J R Stat Soc 1972; 334: 187–220.
24. Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35: 1–39.
25. StartXact user manual. Cambridge: Cytel Software 1992; 5.21–5.26.
26. American Cancer Society. Cancer Facts and Figures—2001. Atlanta, GA, 2001.
27. Komaki R, Seiferheld W, Ettinger D et al. Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small-cell lung cancer: long-term follow-up of RTOG 92-04. Int J Radiat Oncol Biol Phys 2002; 53: 548–557.
28. Arriagada R. Current strategies for radiation therapy in non-small cell lung cancer. Chest 1997; 112 (Suppl 4): S209–S213.
29. Granone P, Cesario A, Margaritora S et al. Morbidity after induction therapy and surgery in non small cell lung cancer (NSCLC). Focus on pulmonary function. Lung Cancer 2002; 36: 219–220.
30. Faber LP, Kittle CF, Warren WH et al. Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer. Ann Thorac Surg 1989; 47: 669–675.
31. Weiden PL, Piantadosi S. Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small-cell lung cancer: a phase II study of the Lung Cancer Study Group. J Natl Cancer Inst 1991; 83: 266–273.
32. Albain KS, Scott CB, Rusch VR et al. for RTOG, SWOG, NCIC, ECOG, CALGB, NCCTG. Phase III comparison of concurrent chemotherapy plus radiotherapy (CT/RT) and CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): initial results from intergroup trial 0139 (RTOG 93-09). Proc Am Soc Clin Oncol 2003; 22 (Abstr 2497).
33. Grunenwald DH, Andre F, Le Pechoux C et al. Benefit of surgery after chemoradiotherapy in stage IIIB (T4 and/or N3) non-small cell lung cancer. J Thorac Cardiovasc Surg 2001; 122: 796–802.
34. Choi NC, Carey RW, Daly W et al. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. J Clin Oncol 1997; 15: 712–722.
35. Sherman DM, Neptune W, Weichselbaum R et al. An aggressive approach to marginally resectable lung cancer. Cancer 1978; 41: 2040–2045.
36. ALPI/EORTC-LCG investigators. Final report of the Adjuvant Lung Project Italy (ALPI): an Italian/EORTC-LCG randomised trial of adjuvant chemotherapy in completely resected non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2002; 21 (Abstr 1157).
37. Keller SM, Adak S, Wagner H et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000; 343: 1217–1222.
38. IALT Investigators. Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2003; 22 (Abstr 6).
39. Robnett TJ, Machtay M, Stevenson JP et al. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. J Clin Oncol 2001; 19: 1344–1349.
40. Trodella L, Granone P, Valente S et al. Phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with inoperable non-small-cell lung cancer. J Clin Oncol 2002; 20: 804–810.
41. Trodella L, Cortesi E, D'Angelillo RM et al. Concurrent radiochemotherapy with weekly gemcitabine in IIIAN2 non-small cell lung cancer: analysis of an ongoing phase II trial. Proc Am Soc Clin Oncol 2003; 22 (Abstr 2713).
42. Strauss GM, Herndon JE, Sherman DD et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: report of a Cancer and Leukemia Group B phase II study. J Clin Oncol 1992; 10: 1237–1244.