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Original Paper

Pre-operative Chemoradiotherapy in Non-small Cell Lung Cancer Stage III Patients. Feasibility, Toxicity and Long-term Results of a Phase II Study

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The aim of this study was to evaluate the feasibility, the response rate and the effect on survival of full dose polychemotherapy delivered concurrently with bifractionated radiotherapy at a radical dose, in a subset of patients with marginally resectable or unresectable stage IIIA-B non-small cell lung cancer (NSCLC). Treatment consisted of two courses of cisplatin 100 mg/m^2 for 1 day plus etoposide 120 mg/m^2 for 3 days delivered from day 1 to day 22, plus radiotherapy delivered in two cycles of 2560 cGy each from day 3 to day 12 and from day 24 to 33 (total dose 5120 cGy in 31 days). The daily dose was 320 cGy in two equal fractions. After surgery, three additional courses of cisplatin plus etoposide were planned. From February 1988 to June 1991, 39 patients with stage III NSCLC (19 were judged as having marginally resectable, 20 as having unresectable disease) were entered into the study. Out of 39 patients (22 squamous cell carcinoma, 17 adeno/large cell carcinoma), 24 had stage IIIa (62%) and 15 stage IIIb (38%). Median PS was 80 (70–90). A total of 78 (74 evaluable) concurrent cycles of pre-operative chemoradiotherapy were delivered. The prominent side-effect was leucopenia: leucopenia ⩾ grade 3 at nadir occurred in 20 cycles (27%), thrombocytopenia ⩾ grade 3 at nadir in seven cycles (9%). 19 patients (54%) had a treatment delay of 1 week between the two cycles. Other important toxicities were sepsis in 5 patients (13%), oesophagitis > grade 2 in 9 patients (23%) and pneumonitis in 5 patients (13%). The response rate was 67% (6 CR (complete response), 16%; 19 PR (partial response), 51%). A resection was subsequently performed in 20 (51%) patients: 14 out of 19 marginally resectable (74%) and 6 out 20 initially unresectable (30%) patients. One other patient had an exploratory thoracotomy. Surgical specimens were tumour-free in 3 patients (14%); in 8 patients (38%) only microscopic tumour was found, and in 10 (48%) macroscopic residual tumour was found. Out of 23 patients attaining a CR, 5 relapsed locally and 11 only distantly. At present, with a follow-up ranging from 64 to 90 months, 34 patients have died, 1 is alive with recurrent disease and 4 (17%) are alive without evidence of disease. Median survival was 16 months, with 18% 3-year survivors and 13% 5-year survivors. Resected patients had a median survival of 21 months, versus 10 months for unresected patients ($P = 0.01$). No significant difference was evident between stage IIIa and stage IIIb patients. Copyright © 1996 Elsevier Science Ltd

Key words: NSCLC, marginally resectable, unresectable, locally advanced, pre-operative treatment, concurrent chemoradiotherapy, hyperfractionated radiotherapy, cisplatin, etoposide

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INTRODUCTION

DESPITE THE high incidence of non-small cell lung cancer (NSCLC), overall curability remains low. Currently, the overall 5-year survival ranges from 10 to 13% and complete surgical resection is the only method of treatment likely to result in cure. Surgery is the first choice of therapy for patients with clinical stage I and II NSCLC, with 5-year survival rates up to 70% in these very limited stages. There is still controversy about treatment of stage III NSCLC patients, and the role of surgery is not well defined. There are subsets of stage III patients whose tumours are amenable to complete resection (e.g. T3N0M0, invading the chest wall), and who achieve a survival rate similar to that of stage II patients [1]. Martini and associates reported a 30% 5-year survival in resected patients with microscopic N_2 disease. However, only 9% of those patients designated as having clinical N_2 reached a 5-year survival, little different from that achievable with radiotherapy alone [2]. Radiation therapy both alone and before surgery in potentially resectable patients has produced poor results, with approximately 5–8% 5-year survival [3, 4]. Two randomised studies of radiotherapy combined with platinum-based chemotherapy regimes in stage III inoperable patients have shown a significant advantage for the combination arm [5, 6]. The aim of our pilot study was to evaluate the feasibility and the response rate of full dose polychemotherapy delivered concurrently with bifractionated radiotherapy given at a radical dose, in a subset of patients with marginally resectable or unresectable stage IIIA or -B NSCLC. The adoption of a daily bifractional radiation scheme is based on the possibility of administering a higher dose over a relatively short period of time (less than 5 weeks), and thus to offer surgical treatment earlier. Other relevant objectives were the resectability rate, the pathological response to induction treatment, the pattern of recurrences and the effect of this combined treatment approach on survival.

PATIENTS AND METHODS

Between February 1988 and June 1991, 39 patients affected by histologically proven NSCLC entered this phase II study. All patients had clinical stage IIIA or IIIB tumours, according to the TNM classification [7].

Eligibility criteria

Eligibility criteria were age ≤ 70 years, a Karnofsky performance status (PS) ≥ 70, weight loss $< 5\%$ in the previous 3 months, no previous cytotoxic treatment, no prior malignancies within the previous 5 years except for non-melanoma skin cancer. Patients had to have evidence of adequate renal, hepatic, cardiac and haematological functions. Prior to beginning primary treatment, all patients were classified as marginally resectable or unresectable. All patients gave informed consent indicating they were aware of the investigatory nature of the treatment.

Staging procedures

Each patient had a chest X-ray, bronchoscopy, chest and upper abdomen CT scan, bone scan, brain CT scan, lung function tests, a complete blood count and biochemical profile. In evaluating chest CT scans, mediastinal lymph nodes were considered negative when < 10 mm and positive when > 20 mm in larger diameter. When lymph nodes were between 10 and 20 mm, a mediastinoscopy was performed.

Restaging procedures

After the chemoradiotherapy induction treatment, all patients underwent a bronchoscopy and a chest and upper abdomen CT scan in order to assess response.

Operability criteria

Patients were defined as operable if able to undergo a complete resection of the primary tumour and a complete mediastinal lymphadenectomy. Adequate pulmonary and cardiac function tests were required.

The disease was considered marginally resectable when only local invasion of the chest wall very close to the vertebral column or central structures occurred or when the tumour infiltrated the carina. Mediastinal lymph nodes had to be ipsilateral without capsular invasion or fixation to central structures. Unresectability was correlated to extensive invasion of chest wall site close to the vertebral column, or of the diaphragm or central structures, by ipsilateral mediastinal lymph nodes with capsular extension and fixation to central structures or by contralateral lymph node involvement. Supraclavicular lymph nodes, vertebral body involvement and malignant pleural effusion were considered as exclusion criteria.

Study design

Patients underwent two courses of chemotherapy (cisplatin (P) 100 mg/m^2 and etoposide (E) 120 mg/m^2 $\times$ 3 days) with a 3-week interval. Radiotherapy was started on day 3 of each cycle of chemotherapy and consisted of 2560 cGy over 8 days, with two daily fractions of 160 cGy each

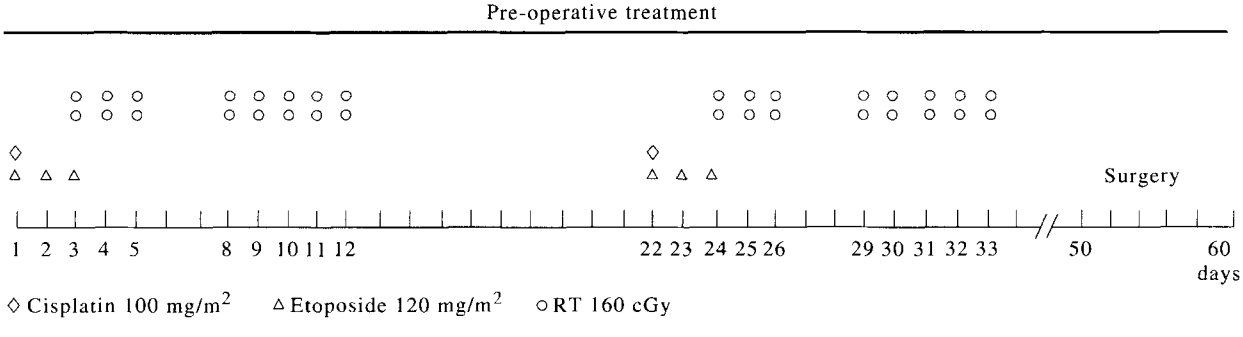

Figure 1. Pre-operative treatment schedule.

and with at least a 5-h interval between each fraction (Figure 1). If patients presented toxicity at subsequent cycles, a 1-week delay was allowed. After two courses, patients were re-evaluated with bronchoscopy plus chest and upper abdomen CT scan in order to assess response. Response and toxicity were evaluated according to World Health Organization (WHO) recommendations on reporting results of cancer treatment [8]. All patients with an objective response or marginally resectable patients with stable disease underwent surgery and then three courses of adjuvant cisplatin plus etoposide (PE) every 3 weeks, starting 3 weeks after surgery. Marginally resectable patients progressing under treatment or inoperable patients with stable disease were not resected. Cytotoxic treatment was stopped in these patients, who received regular check-up procedures only. Follow-up included a physical examination, blood tests and a chest X-ray every 3 months during the first 2 years and then every 6 months. A chest and upper abdomen CT scan was obtained every 6 months during the first 3 years and then once a year.

Radiotherapy

Radiation therapy was administered with a high energy linear accelerator 10 MV unit. The clinical target volumes (CTV) were determined by radiographs and CT scans and included the primary tumour, the ipsilateral hilum and the mediastinum for stage IIIA patients, plus the contralateral hilum for stage IIIB patients. The supraclavicular lymph nodes were not electively irradiated. Radiation was delivered through two large shaped opposing antero-posterior fields for the first part and through two or three oblique fields for the second part. Spinal cord doses were maintained at or below 3750 cGy. The dose was specified at ICRU reference point (according to ICRU report 50) [9].

Statistical analysis

Survival time was calculated from the date chemotherapy was started until death, by the Kaplan–Meier method. The log-rank test was used to compare survival curves.

RESULTS

From February 1988 to June 1991, 39 patients were enrolled in this phase II study. Table 1 provides a summary of clinical patient characteristics at diagnosis. Fifty-six per cent of the patients had squamous cell and 44% adeno- or large-cell carcinomas; 62% had a IIIA and 38% a IIIB tumour; 49% had marginally resectable and 51% unresectable disease. In accordance with our staging procedures, bronchoscopy and chest and upper abdomen CT scans were performed in all patients; a staging mediastinoscopy was performed in 17 of them (44%).

Induction treatment

Seventy-four out of the 78 planned courses (95%) of induction chemoradiotherapy were delivered. 4 patients did not complete the induction treatment because of early death in 3 patients and refusal in one patient. The median duration of the complete induction treatment was 37 days. Haematological toxicity at nadir, as shown in Table 2, was moderate with only 14% grade 4 leucopenia. 19 out of 35 patients (54%) needed a 1-week delay because of myelotoxicity or infections. The most frequent severe non-haematological toxicity (> grade 2 on the WHO scale) was oesophagitis in 9 patients (23%); 2 patients (5%) experienced nephrotoxicity and 5 (13%) pulmonary toxicity. 5 patients (13%) had a severe infection, 1 of whom died of septic death.

Table 1. Patient characteristics

No. of patients	39	
Sex (M/F)	37/2	
Median age in years (range)	56	(32–70)
Median PS (range)	80	(70–90)
Histology		
Squamous cell carcinoma	22	(56%)
Adeno/large cell carcinoma	17	(44%)
Stage		
IIIA	24	(62%)
IIIB	15	(38%)
T3 N0-1	2	(5%)
T1-3 N2	22	(56%)
T4 N0-1	8	(21%)
T1-3 N3	7	(18%)
Unresectable	20	(51%)
Marginally resectable	19	(49%)

Clinical response was assessed after the induction treatment by bronchoscopy and chest and upper abdomen CT scan. 2 patients were not evaluable for response, so that response rate was calculated on 37 patients. Six CR (16%) and 19 PR (51%) were obtained, for an overall response rate of 68% (95% confidence interval: 50–82%). 6 patients (16%) had stable disease, and in 3 patients (8%) the disease progressed during treatment. 2 patients (5%) met an early death because of cardiovascular accidents and one patient had a septic death after a bilateral pneumonia; these patients were considered as treatment failures. Late side-effects, evaluated in patients surviving more than 2 years, consisted of severe lung fibrosis in 2 patients and hypoacusis in one patient.

Surgery

A total of 21 patients (54%) out of the 39 entering the study underwent surgery; 20 resections and one exploratory thoracotomy were performed. Out of 19 marginally resectable patients, 14 were actually resected (74%) and 5 were not resected: 2 refused surgery, 1 progressed and 2 had an early death. 8 (40%) of the 20 initially inoperable patients became potentially resectable; 1 of these refused surgery, 1 had exploratory thoracotomy, and 6 were resected. According to stage, 15 IIIA patients (63%) underwent surgery: 10 (66%) had a lobectomy or a bilobectomy, 5 (33%) had a pneumonectomy. In stage IIIB, 6 patients (40%) underwent surgery: 3 lobectomies, 2 pneumonectomies and 1 exploratory thoracotomy were performed; one patient

Table 2. Haematological toxicity evaluated at nadir in the 74 delivered cycles of concurrent chemoradiotherapy

WHO grade	1	2	3	4
Leucocytes	7 (9%)	7 (9%)	10 (14%)	10 (14%)
Haemoglobin	11 (15%)	9 (12%)	6 (8%)	—
Platelets	8 (11%)	6 (8%)	5 (7%)	2 (3%)

refused the suggested pneumonectomy. Among the 20 resected patients, a total of 17 radical resections (85%) were performed. Overall, 17 out of 39 eligible patients (44%) had a radical resection.

Of the 17 radically resected patients, a pathological complete response (i.e. no residual tumour found in the surgical specimen on primary and on mediastinal lymph nodes) was obtained in 3 patients (3/21, 14%). The pre-operative clinical response was 1 CR and 2 PR. Of the other 14 radically resected patients, 8 patients (8/21, 38%) had microscopical tumour found in the surgical specimen; in 3 of them, tumour was found only on the primary site. The pre-operative clinical response was 1 CR, 5 PR and 2 SD (stable disease). Another 6 patients out of the radically resected group, plus 4 non-radically resected patients (in total 10/21 patients, 48%) had macroscopic residual tumour found in the surgical specimen. In all patients, a pre-operative clinical partial response was obtained.

Post-surgical complications were frequent: 2 patients had pulmonary failure and one of them, a 70-year old male, subsequently died; 2 patients experienced cardiac arrhythmias; 1 patient had a lung abscess; 1 patient had a bronchopleural fistula, underwent an open-window thoracostomy and subsequently died. Surgery-related complications thus occurred in 6 patients (29%) and surgery-related deaths were 2/21 (10%).

Postoperative chemotherapy

The planned postoperative chemotherapy was given to 18 patients (78%) out of the 23 patients in clinical CR after locoregional treatment. 2 other patients not amenable to surgery and in partial response after induction treatment were submitted to the planned three cycles of chemotherapy without any improvement in local disease control.

Pattern of treatment failure

Sites of first relapse in the 23 patients attaining a clinical CR after locoregional treatment (17 radically resected, 3 non-radically resected and 3 inoperable but in CR after the concomitant chemoradiotherapy) were as follows: 5 patients had local relapse only, 4 of these within the irradiation field; 11 patients relapsed only distantly and in 5 of these (22%) the brain was the only failure site. When we analysed the time to failure with the Kaplan–Meier method, 90% of both local and distant failures occurred within 2 years (Figure 2). 2 patients died after surgery and 1 patient was lost to follow-up. 4 patients are alive without evidence of disease; 1 patient developed a second primary tumour (hepatocellular carcinoma) 3 years after resection.

Survival

At the present time, 34 patients have died, 1 is alive with recurrent disease, and 4 (3 operated and 1 non-operated) are alive without evidence of recurrent disease, with a follow-up ranging from 64 to 90 months. Median survival was 16 months for the overall population with 18% of patients alive at 3 years (Figure 3). As shown in Figure 4, when survival was analysed according to resection, there was a marked difference in survival outcome: resected patients had a median survival of 21 months versus 10 months for unresected patients ($P = 0.01$). No significant survival difference was evident between stage IIIa and stage IIIb patients ($P = 0.32$).

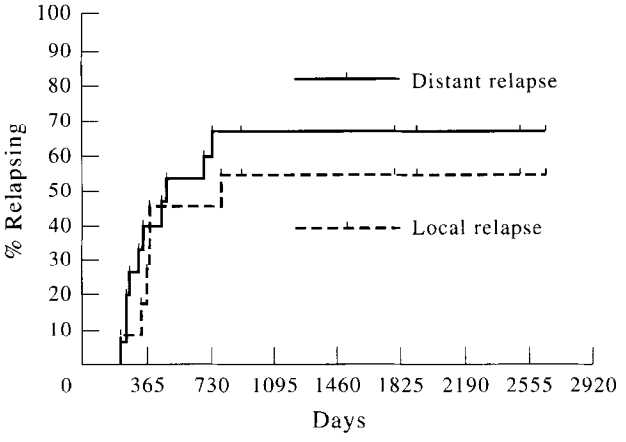

Figure 2. Time to relapse, evaluated by Kaplan–Meier analysis, on 23 patients in complete remission.

DISCUSSION

Stage III NSCLC patients represent a heterogeneous group, with marked differences in survival according to operability and type of regional involvement. There are still no firmly established criteria of operability, and the choice of whether to operate will thus vary from surgeon to surgeon. Stage IIIB patients are generally considered unresectable. Stage IIIA patients are generally considered resectable, marginally resectable or unresectable according to locoregional invasion [10]. In stage III inoperable or marginally resectable patients, surgery or radical radiotherapy are able to produce a 5-year survival rate of about 5%, with the majority of failures occurring both locally and distantly [11]. The purpose of an induction treatment with chemoradiotherapy is to increase local control and at the same time to decrease distant metastases. The pilot studies published so far have only suggested an increased long-term survival, but no clear demonstation has been provided. The majority of pilot studies have been primarily addressed to intermediate endpoints, such as treatment feasibility, increase of resectability rate or clinical and pathological

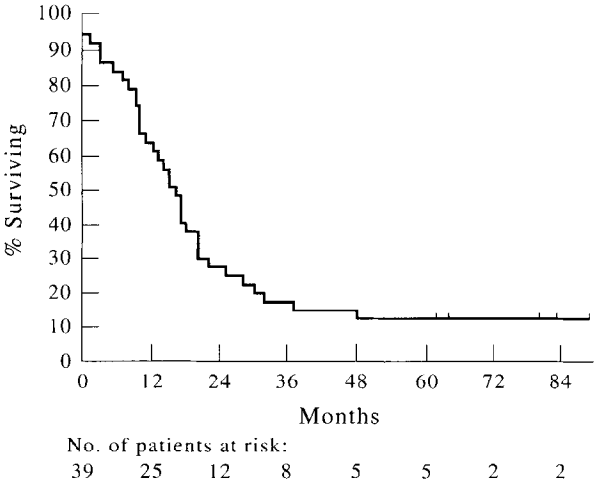

Figure 3. Overall survival estimated by Kaplan–Meier analysis.

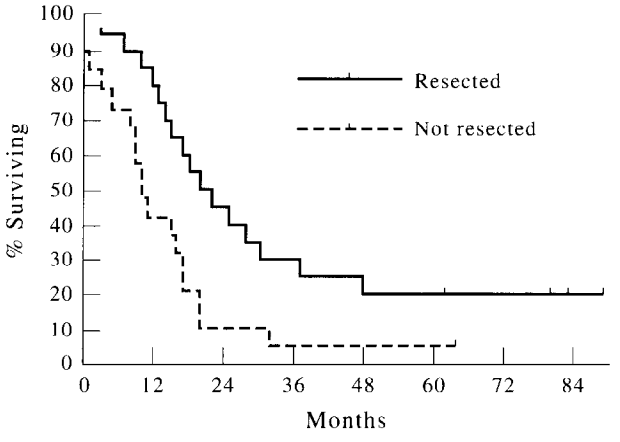

Figure 4. Survival estimated by Kaplan–Meier analysis, according to resection.

response rate. Induction chemotherapy has been shown to be well tolerated, with a clinical response rate of up to 60%, a proportion of resected patients of up to 70% (this probably depending on patient selection) and a pathological CR rate between 5 and 20%. Studies with sequential or concurrent chemoradiotherapy have been planned with the aim of increasing local control as compared with induction chemotherapy alone. In the combined neoadjuvant approach, however, there is the potential risk of administering suboptimal doses of chemotherapy, radiotherapy or both. The aim of this phase II pilot study was to test the feasibility of a complex combined treatment with concurrent chemotherapy and bifractionated radical radiotherapy (5120 cGy in 32 days). We adopted PE as concomitant polychemotherapy, largely because its manageability, its absence of recognised pulmonary toxicity and, as we showed in a previous randomised trial in locally advanced or metastatic disease, its activity is similar to that of a three-drug regimen (PE plus ifosfamide) [12]. The primary aim of our study was achieved, since 95% of the planned concurrent chemoradiotherapy cycles were administered. About half our patients had a 1-week delay between the two neoadjuvant chemoradiotherapy cycles. However, even with this high percentage of delays, we were able to give a potentially radical treatment to the primary and to the mediastinal tumour deposit in a short period time (median 37 days). Although our objective of performing surgery not later than the ninth week was not achieved, 80% of patients were operated on by the twelfth week. This type of concurrent chemotherapy and bifractionated radiotherapy approach seems to obtain a high intensity of induction treatment, and within a period of time which is too short to allow the normal lung tissue to develop fibrotic changes which would impair the surgical procedures. Sixty-three per cent of stage IIIA and 40% of IIIB patients were, in fact, resected. This seems particularly important given the additional fact that no substantial increase in side-effects was observed. For instance, in one of the earliest studies with sequential chemoradiotherapy, a treatment duration of about 4 months was planned with only 30 Gy to be delivered pre-operatively [13]. In three other studies of neoadjuvant chemotherapy plus concurrent radiation with standard fractionation, surgery was planned and in most cases delivered at the eighth week. However, a lower radiotherapy dose (30 Gy plus cisplatin and 5-fluorouracil with or without vinblastine in the first two studies, 45 Gy plus cisplatin and etoposide in the third study) was delivered pre-operatively [14–16]. Our treatment scheme showed a moderate to severe myelotoxicity with 13% life-threatening leucopenia and 1 septic death (3%). Similar results were observed with the sequential chemoradiotherapy approach used by Skarin and associates or with the concurrent radiation plus two-drug chemotherapy approach used by SWOG (12–13% grade 4 leucopenia without fatal events) [13, 15]. In contrast, Strauss and colleagues using a concurrent radiation plus three-drug chemotherapy approach, observed a 39% grade 4 leucopenia and 3 fatal infections (7%) [14]. Although we used split-course radiotherapy, the most frequent non-haematological toxicity was oesophagitis with dysphagia in 23% of cases, a value higher than shown in the previously cited studies.

Our treatment approach proved to be active, with a 67% overall response rate, a proportion similar to that achieved in other studies with stage III patients. We observed among the operated patients 14% pathological CR, with 38% of resected patients showing only microscopic residual disease in carefully evaluated surgical specimens. It is notable that 22% of all patients that obtained a CR relapsed primarily in the brain, and these were 45% of all distant relapses. These data confirm other trials showing high rates of brain relapse, and the need to evaluate prophylactic cranial irradiation whenever a radical approach is performed for stage III NSCLC patients [16, 17]. An important finding of our study is an overall 3-year survival of 18%. Interesting data of the SWOG study showed that, for patients with N_3 disease, the 2-year survival rate was 35% for the subgroup with supraclavicular nodes and 0% for the group with contralateral mediastinal nodes; in our study, patients with supraclavicular node involvement were not included. It is noteworthy that the long-term survivors were almost entirely observed among resected patients ($P = 0.01$). Whether this achievement is actually due to surgery or to patient selection could be determined by a randomised study comparing the combination of chemoradiotherapy with the same followed by surgery.

1. McCaughan BC, Martini N, Bains MS, McCormack PM. Chest wall invasion in carcinoma of the lung. Therapeutic and prognostic implications. *J Thorac Cardiovasc Surg* 1985, **89**, 836–841.
2. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. *Surg Clin North Am* 1987, **67**, 1037–1049.
3. Perez CA, Pajak TF, Rubin P, *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report of the Radiation Therapy Oncology Group. *Cancer* 1987, **59**, 1874–1881.
4. Warram J. For the Collaborative Investigators. Preoperative irradiation of cancer of the lung: final report of a therapeutic trial, a collaborative study. *Cancer* 1975, **36**, 914–925.
5. Arriagada R, Le Chevalier T, Quoix E, Ruffie P, De Cremoux H, Douillard J-Y. ASTRO Plenary: effect of chemotherapy on locally advanced non-small cell lung carcinoma: a randomized study of 353 patients. *Int J Rad Oncol Biol Phys* 1991, **20**, 1183–1190.
6. 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.
7. *Manual for Staging of Cancer* (3rd edn). American Joint Committee on Cancer. Philadelphia, JB Lippincott, 1988.

8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
9. Prescribing, recording, and reporting photon beam therapy. International Commission on Radiation Unit and Measurements, Washington, District of Columbia, 1993.
10. Ginsberg RJ. Limits and perspectives of surgical resection for non-small cell lung cancer. *Lung Cancer* 1991, **7**, 35–39.
11. Perez CA, Bauer M, Edelstein S, *et al.* Impact of tumor control on survival in carcinoma of the lung treated with irradiation. *Int J Rad Oncol Biol Phys* 1986, **12**, 539–547.
12. Paccagnella A, Favaretto AG, Brandes A, *et al.* Cisplatin, etoposide and ifosfamide in non small cell lung carcinoma: a phase II randomized study with cisplatin and etoposide as the control arm. *Cancer* 1990, **65**, 2631–2634.
13. Skarin A, Jochelson M, Sheldon T, *et al.* Neoadjuvant chemotherapy in marginally resectable stage III M_0 non-small cell lung cancer: long-term follow-up in 41 patients. *J Surg Oncol* 1989, **40**, 266–274.
14. 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.
15. Weiden PL, Piantadosi S. For the Lung Cancer Study Group. 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**, 266–272.
16. 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.
17. Jacobs RH, Awan A, Bitran JD, *et al.* Prophylactic cranial irradiation in adenocarcinoma of the lung. A possible role. *Cancer* 1987, **59**, 2016–2019.

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