Induction chemotherapy followed by concurrent chemotherapy and definitive high-dose radiotherapy for patients with locally advanced non-small-cell lung cancer (stages IIIa/IIIb): a pilot phase I/II trial

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Background: Overall prognosis of patients with locally advanced non-small-cell lung cancer (LAD-NSCLC) is still unfavourable. Different attempts to improve treatment results have been made using combinations of chemotherapy and radiotherapy. The aim of this pilot phase I/II investigation was to test the feasibility and toxicity of a definitive multimodality protocol in patients with irresectable NSCLC stages IIIA (N2) and IIIB.

Patients and methods: Thirty LAD-NSCLC patients (stages IIIA/IIIB: 3/27; median age: 54 years, range 34–70; male/female: 17/13) who were consecutively enrolled onto our ongoing neoadjuvant multimodality protocol from October 1996 to February 1999 remained inoperable after induction treatment. Three cycles of cisplatin/etoposide (PE) were followed by hyperfractionated accelerated radiotherapy (HF-RTx; 1.5 Gy bid up to a total dose of 45 Gy in 3 weeks) concurrent with one cycle of PE. Definitive local treatment was completed with a small volume boost of 20 Gy (qd), adding up to a total dose of 65 Gy to the primary. Patients were routinely offered prophylactic cranial irradiation (PCI; 30 Gy; 2 Gy qd).

Results: Overall toxicity of the definitive CTx/RTx protocol—the main endpoint of this investigation—turned out to be acceptable (oesophagitis grade 3/4: 6/4 patients; pneumonitis grade 3/4: 0/1 patients; no treatment-related deaths). Actuarial survival at 2 years was 31% with a loco-regional control rate of 21%.

Conclusions: This regimen turned out to be feasible with acceptable toxicity and will serve as a reference arm in a planned randomised trial in stage IIIB NSCLC, testing the value of surgery in this setting: preoperative induction CTx/RTx followed by surgery versus definitive CTx/RTx.

Key words: combined modality, neoadjuvant, non-small-cell lung cancer, stage III

Introduction

In general, patients with stage III non-small-cell lung cancer experience a poor long-term prognosis due to their multiple—either loco-regional or systemic—risks. Only a small subgroup of patients initially presenting with microscopic disease in one or two ipsilateral mediastinal lymph nodes have a chance of long-term survival following local treatment with surgery alone. These patients may expect 2-year survival rates of between 40% and 50% and 5-year survival rates between 20% and 30% following complete surgical resection with or without adjuvant radiotherapy [1–4]. The remaining majority of patients with bulky, extranodal or multilevel N2-nodes, as well as contralateral mediastinal N3-nodes are generally considered ineligible for upfront surgical approaches. Local treatment with radiotherapy alone has only achieved 2- to 3-year survival rates between 4% and 11% in several randomised trials [5–9]. Recently, an increasing number of phase II and III trials have focused on different combinations of chemotherapy and radiotherapy to improve local control of bulky tumours, but also to decrease the incidence of distant metastases [10]. In particular, the combination of cisplatin-based chemotherapy with thoracic radiotherapy has shown a sub-

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stantial improvement of treatment results in terms of both survival and local control [11–13]. Meanwhile, several investigators have proven the overall feasibility of intensive multimodality protocols, including surgery in patients with primarily irresectable stage IIIA/IIIB tumours, leading to complete resection rates in the range 27% to 81%, while reporting median survival durations between 19 and 26 months; these populations were, however, carefully selected [14–22].

Nevertheless, the effect of combined modality therapy in patients with inoperable stage III NSCLC is an area of continuing clinical research and the selection criteria for patients who profit most from surgery after neoadjuvant CTx/RTx are still unknown. Based on the experience from several multimodality trials, there is strong evidence that patients achieving a pathological complete response (pCR) in the mediastinum and those in whom complete (R0)-resection can be performed following induction, will profit most from definitive surgery with regard to their long-term prognosis. In patients remaining irresectable after preoperative therapy, treatment intent has been considered mainly palliative. Especially for this patient cohort, attempts should be made to develop combinations of local radiotherapy and systemic treatment which are more effective.

Since 1991, our group has conducted a phase II trial of neoadjuvant therapy in patients with stage III non-small-cell lung cancer [21]. Our treatment protocol was based on induction chemotherapy with three cycles of cisplatin/etoposide followed by hyperfractionated accelerated irradiation of the primary tumour and mediastinal lymph nodes concurrent to one further chemotherapy cycle. If possible, following this chemoradiation protocol, surgery was included as the definitive local treatment modality. Here, we report our results of patients who have been entered prospectively from 1996 onwards to the neoadjuvant protocol, but who remained inoperable at the end of induction therapy and instead received additional high-dose boost irradiation to the primary tumour site as an alternative definitive loco-regional treatment.

Patients and methods

Patient selection

All patients had histologically confirmed NSCLC and underwent mediastinoscopy prior to study entry. Only those *not* presenting with minimal N2-disease (one or two lymph nodes microscopically involved) in the mediastinum were included. Further details of the pretreatment evaluation have been reported in our prior pilot study. Obligatory staging procedures were computed tomography (CT) scans of the chest, upper abdomen and brain, abdominal ultrasound, radionuclide bone scan and bronchoscopy. In cases of suspected pulmonary artery invasion, an angiographic CT scan of the thorax was performed, and if still in doubt, diagnosis was confirmed by trans-oesophageal echocardiography. Before treatment initiation, patients were carefully evaluated by an interdisciplinary team that comprised a pulmonologist, a thoracic surgeon, a medical oncologist and a radiation oncologist. Besides staging procedures, cardiopulmonary function tests, lung function testing, ventilation-perfusion nuclide scintigraphy, ECG, stress ECG and echocardiography were performed in order to assess the medical status of each patient and the individual ability to undergo such an aggressive multimodal protocol. The study was approved by the local ethics committee. All patients had given informed consent prior to the start of induction.

Treatment design

All patients were planned for three courses of chemotherapy with cisplatin 60 mg/m^2 intravenously (i.v.) on days 1 and 7 and etoposide 150 mg/m^2 i.v. on days 3, 4 and 5. Cycles were repeated every 22 days unless patients had a white blood cell (WBC) count <2500/µl or a platelet count <100 000/µl. Dose reductions were performed for grade 4 leucopenia or grade 3 leucopenia associated with infection (70% of etoposide dose) or grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding (cisplatin 50 mg/m^2). In the case of reversible creatinine elevations with values between 1.5 mg/dl and 2.0 mg/dl during the interval, the cisplatin dose was reduced to 50% in the next course. If creatinine values increased above that value or seemed to persist, carboplatin 150 mg/m^2 was substituted for cisplatin and treatment was continued. During the tenth week of treatment, the concurrent chemoradiotherapy was started combining hyperfractionated accelerated radiotherapy (1.5 Gy per fraction bid, interfraction interval ≥6 h, 5 days a week, up to a total dose of 45 Gy within a period of 3 weeks) with one cycle of chemotherapy consisting of cisplatin 50 mg/m^2 i.v. on days 2 and 9 (after the start of radiotherapy) and etoposide 100 mg/m^2 on days 4, 5 and 6. During the third week of radiotherapy (preferably when reaching a total dose of at least 39–42 Gy), a re-evaluation of operability and resectability was performed consisting of a chest CT scan (angiographic CT, respectively), and in a few patients, repeat mediastinoscopy. An interdisciplinary panel of medical oncologists, thoracic surgeons and radiation oncologists then decided whether patients were medically or prognostically operable. Patients with persisting positive mediastinal lymph nodes (more than one ipsilateral region: paratracheal, tracheobronchial, subcarinal; or contra-lateral extent) or still with irresectable tumours due to local extent (invasion of pulmonary artery or direct mediastinal invasion) were excluded from surgery. The definitive treatment in those patients with inoperable tumours was completed immediately with a boost irradiation of 20 Gy (conventional fractionation). The full treatment design is shown in Figure 1.

Radiotherapy

Three-dimensional treatment planning was performed in all patients. The planned target volume for the first 45 Gy (PTV2) consisted of the primary tumour with a margin of 1.5–2.0 cm, the ipsilateral hilum, the ipsilateral mediastinal and the subcarinal lymph nodes up to 4.5 cm below the carina with a margin of 0.5–1.0 cm. For N2-disease, the contralateral paratracheal and bronchopulmonal nodes were included with a margin of 0.5 cm. For tumours of the upper lobes with extensive ipsilateral mediastinal involvement, the ipsilateral supraclavicular region was also irradiated. The first 30 Gy were given by anteroposterior–posteroanterior (ap–pa) fields with 10 MV or 15 MV photons. In order to keep the total dose to the spinal cord below 42 Gy, radiotherapy after 30 Gy was continued employing an isocentric two-field wedge technique that consisted of an ap-field and an ipsilateroposterior oblique field. Customised blocks or multi-leaf-collimation were used to increase beam conformality.

Beyond 45 Gy, the boost volume (PTV1) was tailored to the primary tumour and the macroscopically involved mediastinal nodes of the next node level (centrally located tumours) with a safety margin of 1.0 cm. The

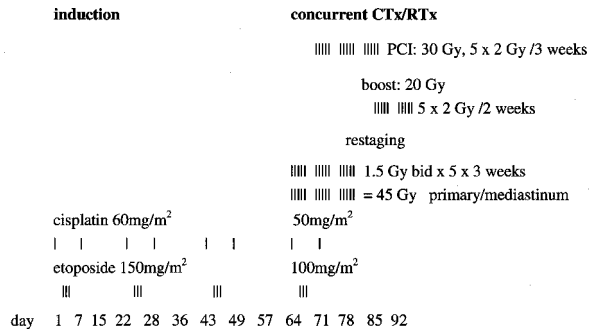

Figure 1. Study design.

maximum dose to the spinal cord was limited to 42 Gy, the mean total lung dose (both lungs regarded as whole organ at risk) was kept below 20 Gy (maximum 25 Gy), if possible.

After 45 Gy was given in fractions of 1.5 Gy twice daily, irradiation of the primary tumour was continued with 20 Gy given in conventional fractionation (2 Gy, five times per week) up to a total dose of 65 Gy. The target volume was treated using parallel opposed oblique fields or wedge compensated fields if indicated, to limit organ toxicity (heart, lungs).

In order to reduce treatment interruptions after re-evaluation (see above) the entire radiotherapy treatment planning was performed as early as possible (in nearly all patients during the first 3 weeks).

Patients were routinely offered prophylactic cranial irradiation (PCI), which was started after the end of the fourth chemotherapy cycle, regularly at day 9 of the thoracic irradiation. A total dose of 30 Gy was given in daily fractions of 2 Gy to the brain and the meninges above the foramen magnum. A helmet technique was used to include the basal parts of the temporal lobes. The target volume was treated with opposed lateral isocentric fields (cobalt 60 or 5 MV linear accelerator).

After completion of treatment, patients showed up for follow-up investigations every 3 months during the first 2 years. A CT scan of the chest was performed, as well as liver ultrasound, and laboratory tests including pulmonary function testing where necessary (in case of suspected relapse). Treatment-related side effects and complications were assessed using the Common Toxicity Criteria [23, 24].

Statistical analysis

Statistical analysis was performed using the SAS statistical software package [25]. Overall survival was calculated from the first day of induction chemotherapy until death, loss to follow-up or end of follow-up at the time of evaluation for this report (1 April 2001). Progression-free survival and time to loco-regional relapse were calculated from the first day of induction chemotherapy until disease progression (loco-regional failure or distant metastasis) or loco-regional relapse, respectively. Survival curves were calculated according to the method described by Kaplan and Meier [26].

Results

Patient selection and characteristics

From October 1996 to February 1999 109 patients were entered onto our phase II study on neoadjuvant radiochemotherapy (RT/CT). Patient characteristics are given in Table 1. All patients received induction chemotherapy and hyperfractionated accelerated thoracic radiotherapy. One patient discontinued treatment due to a decline in performance status. Three patients progressed with their disease during induction therapy. Of these, one patient developed malignant pleural effusions, two patients had pulmonary metastases. Thus, 105 patients completed induction RT/CT. Nine patients from this group were found to be inoperable due to contralateral mediastinal involvement at the time of repeat mediastinoscopy but refused continuation of radiotherapy and were offered palliative chemotherapy. One further patient had an explorative thoracotomy and was evaluated as irresectable, intraoperatively.

Table 1. Patient characteristics

Characteristic	Entire group		High-dose radiotherapy group	
	No.	(%)	No.	(%)
	109	(100)	30	(100)
Stage IIIA	24	(22)	3	(10)
Stage IIIB	85	(78)	27	(90)
Age (years)				
Median	56		54	
Range	35–72		34–70	
Sex				
Male	80	(73)	17	(57)
Female	29	(27)	13	(43)
Histological cell type				
Squamous cell	50	(46)	13	(43)
Adenocarcinoma	47	(43)	13	(43)
Large cell	12	(11)	4	(14)

Table 2. Stage distribution of high-dose radiotherapy group

	No. of patients	(%)
T2 N2	2	(7)
T3 N2	1	(3)
T2 N3	5	(17)
T3 N3	2	(7)
T4 N0	1	(3)
T4 N2	11	(37)
T4 N3	8	(26)

Sixty-five patients (60%) were operated on with a curative intent.

The remaining 30 patients were referred to radiotherapy in order to complete local treatment within a pilot phase I/II radiotherapy boost protocol. They form the cohort of the present investigation. Median age was 54 years (range 34–70 years), median follow-up 40 months (range 26–54 months). All patients had stage III NSCLC proven by biopsy (stage IIIA, three patients; stage IIIB, 27 patients) and completed the full course of treatment. Pretreatment histological subtyping included 13 (43%) squamous cell carcinomas, 13 (43%) adenocarcinomas and four (14%) large-cell carcinomas. The stage distribution of this group is given in Table 2.

Treatment

The mean dose to the primary tumour region was 64.8 Gy (64–66 Gy). Three patients refused prophylactic cranial irradiation. Two patients had a history of neurological disorders, three other patients had known cerebral arteriosclerosis (with history of minor stroke symptoms) and therefore did not receive PCI. Altogether, PCI was given to 22 out of a total of 30 patients

Two patients with T2N2-tumours were inoperable for medical reasons (one due to coronary heart disease with consecutive heart failure; the other had deteriorating pulmonary function tests with severe obstruction, thus a planned pneumonectomy could not be performed), one patient with a T3N2-tumour had remaining mediastinal involvement (>1 level) confirmed by mediastinoscopy and was excluded from surgery. From the group with stage IIIB tumours, 12 patients were not resected because persistent centrally located mediastinal tumour masses were found at the repeat chest CT scan following induction chemoradiotherapy (45 Gy). Two patients underwent repeat mediastinoscopy but showed positive lymph node involvement of two mediastinal levels and were therefore excluded from thoracotomy. One patient was taken to thoracotomy, but resection with curative intent could not be performed due to extensive loco-regional tumour infiltration. Ten patients were excluded from surgery due to persistent involvement of the pulmonary artery, two patients refused surgery after induction chemotherapy.

After completion of induction chemotherapy and chemoradiotherapy, only six patients had a treatment break (range 3–28 days; mean 14 days) until boost irradiation was restarted, all others experienced no treatment delay or interruption. Thus, the entire treatment was completed within 35–37 days in 24 patients. In two patients the overall treatment time was 38 and 40 days, in four patients, overall treatment time exceeded 45 days (maximum 63 days).

Partial response to induction chemotherapy was found in 14 (47%) cases. Minor response and stable disease (no change) was found in 10 (33%) and six (20%) cases, respectively. Thus, ~80% of the patients showed some kind of reduction of their tumour volume.

Toxicity analysis

Haematological toxicity observed during induction chemotherapy was moderate. Maximum toxicities of induction chemotherapy as well as of the combined chemoradiation are given in Table 3. One patient developed pneumonia during combined chemoradiotherapy, but recovered shortly following treatment with antibiotics. Treatment breaks due to haematological toxicity were neither necessary during induction chemotherapy nor during combined modality treatment.

During concurrent treatment with chemoradiation, oesophagitis was the major acute type toxicity. Grade 1 and 2 oesophagitis were found in eight (30%) and 12 (40%) cases, respectively. Grade 3 oesophagitis was diagnosed in six (20%) cases, grade 4 (requiring short-time parenteral nutritional support) in four (13%) patients.

Radiation-induced pneumonitis was assessed as grade 1 in 20 (67%) patients, grade 2 in nine (30%) patients, grade 4 in one patient (3%). Ten weeks after completion of the combined chemoradiotherapy, the latter patient developed severe radiographic and clinical signs of pneumonitis requiring oxygen supplementation and later also required assisted ventilation. It finally turned out that this patient had extensive disease progression and ultimately died of malignant pericardial effusions rendering this toxicity evaluation difficult.

Survival data

At the time of this analysis (1 April 2001), the median overall survival duration was 13 months [95% confidence interval (CI) 10 to 18 months; Figure 2]. The actuarial 2-year survival rate was 31% (95% CI 13% to 49%). For patients with squamous cell carcinomas, adenocarcinomas, and large cell carcinomas, a median survival of 18, 11, and 22 months, respectively, was observed. According to nodal status patients with contralateral mediastinal involvement (N3) experienced shorter survival times. Median survival in the N3-group was 10 months (95% CI 8 to 27 months), 1-year survival 36% (95% CI 11% to 61%), while those patients without nodal involvement or N2-disease had a median survival of 18

Table 3. Toxicity during induction chemotherapy (n = 30) and combined chemoradiation (n = 30)

Toxicity	CTC score				
	0	1	2	3	4
(1) During induction chemotherapy					
Haematological	No.				
Leucocytopenia	1	3	13	13	0
Thrombocytopenia	8	7	8	7	0
Anaemia	0	5	22	3	0
Non-haematological					
Nausea/vomiting	0	16	10	4	0
Fever/infection	0	24	6	0	0
(2) During combined chemoradiation (n = 30)					
Hematological	No.				
Leucocytopenia	1	3	7	19	0
Thrombocytopenia	4	11	8	7	0
Anaemia	0	3	23	4	0
Non-haematological					
Nausea/vomiting	0	11	13	6	0
Fever/infection	0	26	3	1	0
Oesophagitis	0	8	12	6	4
Pneumonitis	0	20	9	0	1

months (95% CI 11 to 21 months) and 1-year survival of 69% (95% CI 43% to 95%). Patients with T4-tumours experienced a median survival of 13 months (95% CI 11 to 27 months).

Median disease-free survival for the entire group was 9 months (95% CI 7 to 11 months) and the 2-year disease-free survival rate was 11% (95% CI 0% to 25%; Figure 3). Patients with squamous cell carcinoma had a median progression-free survival of 11 months compared with 7 months for patients with adenocarcinoma and 15 months for patients with large cell carcinoma.

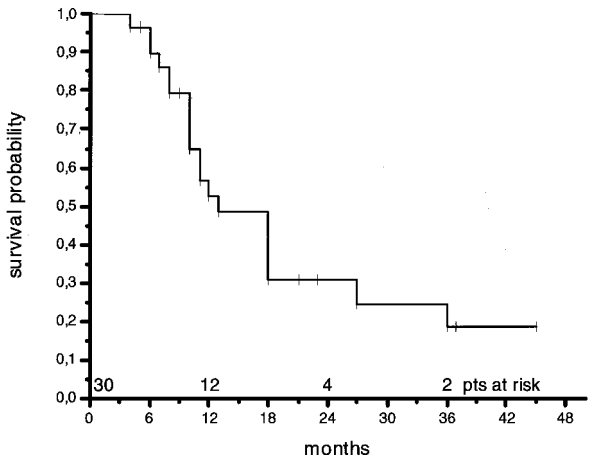

Figure 2. Overall survival of all patients (tick marks represent censored patients).

Pattern of failure

Up to the last follow up, 22/30 patients (73%) have shown disease progression. Local recurrence (at the primary tumour site) as the isolated site of first failure was seen in eight patients, five of them developed distant metastases later in the course of their disease. First sites of failure are given in Table 4. Five patients had regional (mediastinal lymph node) failure as the first site of relapse. The actuarial loco-regional control rate (at primary tumour site and mediastinal lymph nodes) after a median follow-up period of 2.5 years remains 21% (median time to loco-regional relapse: 12 months; Figure 4). Overall, systemic disease progression was observed in 19 out of 22 patients. Ten of these showed ongoing local control at the primary tumour site.

Brain metastasis as the site of first relapse was found in three patients. Following administration of PCI, only one out of 22 (5%) patients experienced brain metastasis as the first relapse site. Two out of eight (25%) patients without PCI developed brain metastasis as their first relapse.

Discussion

The aim of the present investigation was to evaluate the feasibility, toxicity and safety of an intensive definitive chemo-radiotherapy protocol in patients remaining inoperable following a bimodality induction, either due to persistent

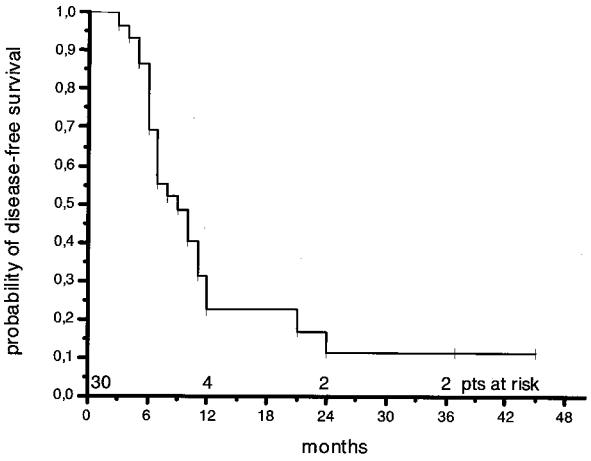

Figure 3. Disease-free survival of all patients (tick marks represent censored patients).

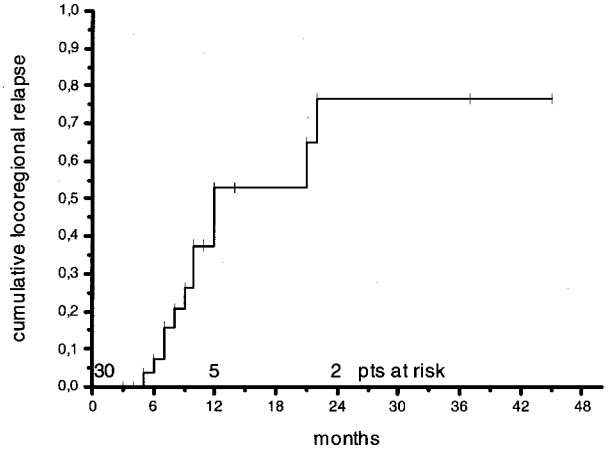

Figure 4. Actuarial probability of loco-regional relapse (primary tumour region and mediastinum, tick marks represent censored patients).

multiple N2-lymph nodes, contralateral mediastinal N3-nodes or bulky irresectable T4-tumours infiltrating major mediastinal structures. Following three cycles of chemotherapy, as well as concurrent chemoradiation with accelerated hyperfractionated radiotherapy up to a dose of 45 Gy, a small-volume boost of 20 Gy was given to the primary tumour, adding up to a total radiation dose of 65 Gy. The full course of this radiotherapy schedule could be delivered without significant treatment delays. No treatment-related death occurred in this series. Besides moderate haematological toxicities, a carefully performed analysis revealed 10 patients with—usually short term—grade 3 or 4 oesophagitis and one with grade 4 pneumonitis. Thus, this programme can be considered to have an overall moderate and acceptable toxicity profile.

Treatment intensification by adding chemotherapy to thoracic irradiation has not generally led to enhanced toxicities within different concurrent chemoradiation protocols. The West Japan Lung Cancer Group conducted a multicentre phase III trial comparing concurrent versus sequential thoracic radiotherapy in combination with the mitomycin, vindesine and cisplatin (MVP) regimen [27]. In the concurrent arm, conventionally fractionated radiotherapy started on day 2 up to a dose of 28 Gy (2 Gy, five fractions per week) followed by a resting period of 10 days. Following this short break, radiotherapy was continued up to a total dose of 56 Gy. In the sequential arm, radiotherapy was delivered after completing two courses of chemotherapy and consisted of 56 Gy given in 5.5 weeks (2 Gy per fraction). If grade 4 radiation-induced oesophagitis occurred, radiotherapy was interrupted until oesophagitis improved to at least a severity of grade 3 or less. The incidence of severe oesophagitis (grade ≥3) was not recorded to be different in both arms and accounted for only three and four cases in the trial, respectively. Pulmonary toxicity (grade ≥3) was observed only in two cases within each arm. Enhanced toxicities may have been avoided in this study by the chosen split-course irradiation in a conventional fractionation scheme, reduced total radiation doses and pre-planned treatment delays if higher grade toxicities occurred.

Table 4. Site of first failure in patients with relapse (n = 22)

Localisation	No. of patients	(%)
Loco-regional	13	(60)
Pulmonary metastases	2	(9)
Bone	4	(18)
Brain	3	(14)

Ardizzoni et al. [28] have tested a protocol of induction chemotherapy, comparable to that in the Cancer and Leukemia Group B (CALGB) 8433 trial, followed by standard radiotherapy combined with daily low-dose cisplatin, comparable to the European Organization for Research and Treatment of Cancer (EORTC) schedule [6, 9]. Thoracic radiation started on day 43 of the treatment protocol delivering a total dose of 60 Gy in 6 weeks. Cisplatin was given at a daily dose of 5 mg/m^2. Although oesophagitis was frequently observed during the time of chemoradiation (22/28 patients), it was graded severe only in two patients (7%). In their trial, one patient developed severe radiation-induced pneumonitis and died from global respiratory failure.

On the basis of radiobiological considerations, different investigators have introduced complex alternative fractionation schedules into the treatment of locally advanced NSCLC in order to further intensify the local efficacy of radiotherapy. However, increased acute treatment toxicities have frequently served as strong arguments against these aggressive protocols. Continuous hyperfractionated accelerated radiotherapy (CHART) is probably the most condensed way of treatment acceleration, delivering a total radiation dose of 54 Gy in only 12 consecutive days [29]. In this series by Saunders et al. [29],

treatment-related morbidity was confined to dysphagia which occurred in the CHART arm sooner and with more severity than following conventional fractionation. With CHART, 19% of patients experienced grade 3 oesophagitis whereas radiation-induced pneumonitis was more pronounced in the conventional arm of that study. However, in that trial setting, no concurrent chemotherapy was included.

In a multicentre phase II study, the Radiation Therapy Oncology Group (RTOG) enrolled 79 patients onto a protocol of hyperfractionated accelerated radiation therapy (1.2 Gy bid, total dose 69.6 Gy). Patients received two concurrent cycles of cisplatin and oral etoposide. The rate of severe oesophagitis (grade ≥3) was 53% among 76 eligible patients, of whom only 53 (70%) completed chemotherapy as planned. Grade ≥3 lung toxicity was reported in 19 patients (25%) and accounted for two of three treatment-related deaths [30]. The data of the corresponding follow-up phase III investigation of this concept have recently been presented [31]. In a large three-arm randomised phase-III comparison run by the RTOG, the rate of local control could be significantly increased by the use of concurrent chemoradiotherapy and even more by including hyperfractionated accelerated radiotherapy in comparison to a standard sequential schedule of chemotherapy and radiation. However, while survival could be significantly prolonged in the arm with concurrent chemoradiation, the improvement in local control with bid radiotherapy did not transfer into better survival results within the third comparative arm. This may partly be attributed to the inclusion of oral etoposide into that arm and furthermore by the chosen small-fraction doses of 1.2 Gy. Toxicity results of both concurrent chemoradiation arms with conventional fractionation, as well as with concurrent twice-daily irradiation, were overall moderate and acceptable even in the multicentre setting.

Jeremic et al. [32] conducted a three-arm trial with hyperfractionated radiotherapy (1.2 Gy bid, total dose 64.8 Gy) either alone or in combination with carboplatin and etoposide given during the first, third and fifth treatment week. The incidences of acute grade 3 or 4 toxicities were most pronounced in the concurrent arms and were found at rates of 17% and 27%, respectively [32].

Compared to these concurrent chemoradiation protocols including various chemotherapy regimen, different radiation fractionation schedules and doses, our protocol was found to be moderately toxic and could be applied safely to all patients. So far, a 2-year survival rate of 31% and a median overall survival of 13 months appear to be acceptable in comparison to the results of other published series in patients with NSCLC stages IIIA/IIIB with mainly positive selection criteria [8, 9, 29]. However, with the median follow-up of patients alive now exceeding 31 months at the time of this report, survival data for the trial population have to be interpreted with caution.

Non-invasive restaging procedures following induction therapy are a critical point in the neoadjuvant treatment setting. Whether performing tomographic studies, either employing chest CT scans or MRI, shortly after completion of induction, allows for a meaningful preoperative evaluation remains debatable. In the future, the use of positron emission tomography with 18-fluorodeoxyglucose will possibly offer significant advantages in assessing tumour response and predicting the chance of curative resection [33]. Choi and coworkers demonstrated that with PET even the definition of the high-dose boost irradiation target volume will be facilitated.

The inclusion of surgery into multimodality treatment protocols with the aim of definitive local control in patients with locally far advanced NSCLC stage IIIB is a continuing matter of controversy and one of the major issues in this stage group. For these patients an individualised conformal radiotherapy boost may represent a reasonable alternative treatment option. Three-dimensional radiation therapy planning may offer the possibility of further dose escalation and reaching total doses of up to 75 Gy might improve local control rates.

Furthermore, the efficacy of local and systemic treatment may be enhanced with the use of newer cytotoxic drugs, e.g. paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, which have all been introduced in the treatment of NSCLC with considerable success [34–39].

Therefore, in parallel to the design of the North American Intergroup 0119 trial in stage IIIA(N2) (K. Albain, personal communication) [40], we are planning to start a prospective randomised phase III trial testing the value of surgery in patients with stage IIIA/IIIB disease following concurrent hyperfractionated accelerated chemoradiation up to 45 Gy. After restaging, patients considered to be operable will be randomised to receive either surgery or a conformal high-dose radiotherapy boost. For this latter arm, the present trial will serve as a feasibility and toxicity pilot investigation.

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