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Original Paper

Comparison of Induction Chemotherapy Before Radiotherapy with Radiotherapy Only in Patients with Locally Advanced Squamous Cell Carcinoma of the Lung

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The aim of this randomised trial was to investigate the effect of induction chemotherapy before radiotherapy on survival in 302 patients with non-resectable squamous cell carcinoma of the lung. Radiotherapy, 56 Gy to the chest, was given to 154 patients and combined treatment, with chemotherapy preceding the radiotherapy, to 148 patients. Chemotherapy consisted of three courses of cisplatin (120 mg/m^2) and etoposide (100 mg/m^2 i.v. for 3 days) administered every fourth week. Median survival was 10.5 months in the radiotherapy arm and 11 months in the combined treatment arm. The 2-year survival rate was 17% in the radiotherapy arm and 21% in the combined treatment arm. Addition of chemotherapy seemed to significantly improve survival, according to the Cox multivariate analysis ($P = 0.04$), but as only a trend according to life-table analysis ($P = 0.11$). Chemotherapy also accomplished a trend towards improved local control ($P = 0.08$) and towards decreased metastatic disease ($P = 0.10$). 2 patients in the combined treatment arm, but none in the radiotherapy arm, died from toxicity. The conclusion was that the value of the chemotherapy used in this study was very modest, but the results strongly support further research for more efficient drugs and combinations. **Copyright © 1996 Elsevier Science Ltd**

Key words: squamous cell carcinoma of the lung, chemotherapy, radiotherapy, survival, local control

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INTRODUCTION

AT DIAGNOSIS, approximately 50% of patients with non-small cell carcinoma of the lung (NSCLC) have stage III disease, that is locally advanced tumours or tumours with mediastinal lymph node metastases (or both), but without distant metastases [1, 2]. Although some of these tumours can be radically resected, surgery has a limited role in these patients that varies between different institutions [3, 4]. Radiotherapy is, in many institutions, considered to be the standard treatment [5–7]. However, this policy has been questioned, as very few cases are cured, with a 5-year survival rate of approximately 5% or less. Squamous cell carcinoma as well as other types of NSCLC generally have limited radioresponsiveness [8] and the probability of achieving local control is higher with an irradiation dose of 50–60 Gy than with lower doses [9].

The responsiveness to drugs has also been considered as low [10], and the routine use of chemotherapy has, as a rule, not been recommended. However, during the early 1980s, when the present study was planned, early results

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with cisplatin combined with etoposide or vindesine were good, with response rates of 25% or more [11, 12].

Such data were considered promising enough by our group to start a randomised study of the hypothesis that the addition of chemotherapy to radiotherapy might improve survival. Our group comprised the majority of institutions for oncology and pulmonary medicine in Sweden that indicated a sufficient inclusion rate of patients to demonstrate, within 3 or 4 years, a 10% improvement in survival. The incidence of lung cancer in Sweden was at the start of the trial, approximately 2500 cases/year, of which 35–40% were squamous cell carcinoma.

The primary aim of the trial was to study survival, and the secondary aim was to study local control, metastases and toxicity. Any favourable effects arising from the chemotherapy were expected to be the result of a reduction in the primary tumour, implying a better chance of achieving local control with the subsequent radiotherapy. A favourable effect from chemotherapy on metastatic disease had not been demonstrated at that time. As the risk of early dissemination of subclinical distant metastases was considered greater in patients with adenocarcinomas or large cell carcinomas, such cases were excluded from the study. It was hoped that this might improve the chances of demonstrating favourable drug effects.

PATIENTS AND METHODS

Patients

The following inclusion criteria were used: age <76 years, a sufficient pulmonary function for radiation treatment (FEV1.0 (forced expiratory volume in 1 second) >1 l), verified squamous cell carcinoma of the lung, limited disease, an inoperable patient or non-resectable tumour (determined with or without surgery), informed consent and a performance status evaluated as Zubrod 0–3 (Zubrod 0: normal activity, 1: symptoms, but patient nearly fully ambulatory, 2: some time spent in bed, but the need to be in bed less than 50% of normal daytime, 3: a need to be in bed greater than 50% of normal daytime, 4: unable to get out of bed) [13].

Tumour stage

The following data were recorded: the size of the tumour as determined using X-rays (if measurable), the result of bronchoscopy, of mediastinoscopy (if performed) and CT scan (if performed). Tumour staging data of the tumour were also reported, performed according to the TMM classification (UICC 1978) during the initial part of the study. After 1987 many patients were classified according to the 1987 UICC classification (Geneva 1987). Re-evaluation was, therefore, performed by one of the authors (OB) according to the latest UICC classification [13].

Treatment

Chemotherapy. Chemotherapy consisted of cisplatin, 120 mg/m^2, administered intravenously on day 1. Prehydration was achieved with 1000 ml glucose solution 2 h before the start of the chemotherapy. Cisplatin was administered with 2000 ml NaCl solution and 500 ml 15% mannitol solution over 4 h. A further 2000 ml was administered over the following 24 h, either orally or intravenously. Etopside, 100 mg/m^2 i.v., was administered on days 1, 2 and 3.

A second course of chemotherapy was given 4 weeks after the first course. If a chest X-ray did not demonstrate tumour progression, a third course was administered after the same time interval. Radiotherapy usually started within 3 weeks of the third course, or in the case of progression, within 3 weeks of the second course.

Chemotherapy was not given if serum creatinine levels were elevated above 130 mmol/l or had risen by more than 30%, compared with the initial value. Etoposide was reduced according to a graded dose reduction schedule, and no drugs were given when leucocyte levels were less than 2.0×10^9/l or thrombocyte levels were less than 10^9/l.

Radiotherapy. Radiotherapy was planned and administered identically in both arms of the study. It was started within 3 weeks in patients in the radiotherapy arm, or 2–3 weeks after the last chemotherapy course in the combined treatment arm.

Planning was carried using the CT scan, and correction was made for air within the lung tissue. The clinical target volume consisted of the gross tumour volume and mediastinal lymph nodes. It was recommended that the planning target volume should include 1.5–2 cm of tissue around the tumour. It was to extend to 5 cm below the carina and upwards to include the supraclavicular nodes. The dose used for the target volume was 2 Gy/day, 5 days a week to 56 Gy, with a split of 2 weeks after 38 Gy. The total treatment time was thus approximately 7.5 weeks. The target volume was preferably retained throughout the whole treatment. However, if the target volume was large, with a high risk for lung toxicity, the margins could be decreased during the latter part of the treatment.

To avoid toxicity, it was recommended that the highest dose to the spinal cord should be 50 Gy and that at least 50% of the normal lung tissue should be excluded. Dose/volume histograms were, however, not routinely performed.

The treatments were delivered with a linear accelerator, but specific recommendations for energy were not made.

Follow-up. Clinical examination and a chest X-ray were to be performed every third month during the first 2 years and after that every sixth month. Patients with metastases or progressive local disease were treated with ordinary palliative therapy. If the doctor responsible for the patient considered chemotherapy to be indicated, cyclophosphamide as a single agent was recommended. Autopsy was recommended whenever applicable.

Response evaluation. The responses were evaluated using chest X-rays. With respect to the difficulties in evaluating these images after irradiation, no distinction was made between progressive disease (PD) and stable disease (SD), but complete response (CR, that is complete disappearance of all visible tumour) or partial response (PR, that is at least a 50% reduction in the tumour area as judged from the images) were distinguished from the PD and SD categories. Most of the CR and PR chest X-ray pictures were verified by one of the group (EN), but in certain hospitals the images were destroyed shortly after the death of the patients.

Local control was defined as sterilisation of all of the tumour at the primary site. Criteria for this were: no tumour at autopsy or a CR combined with survival for more than 4 years, with no evidence of tumour at the primary site.

Cure was defined as the combination of local control, defined as above, and no metastases at autopsy, or survival for more than 4 years with no evidence of disease at the primary site or any metastases.

Statistical considerations and randomisation. Prestudy statistical considerations stated that 332 patients were needed to demonstrate a difference of 10% between the two groups with 95% confidence if survival in one of the groups was 15%. This was expected to prove to be the approximate 2-year survival rate of the control arm. The expected patient inclusion rate indicated that the study could possibly be completed within 3 years.

Stratification was performed for medical care region, thoracotomy without resection and the existence of supraclavicular lymph nodes. Both thoracotomy without resection and supraclavicular lymph nodes were considered to be poor prognostic signs, constituting the basis for stratification.

One interim analysis was planned for approximately 2 years into the study, with respect to the risk of excessive death in either of the treatment arm; this was performed and no difference between the arms was found.

The randomisation procedure was accomplished with a telephone call to the Regional Oncological Centre in the Uppsala region. Forms were completed by the doctor responsible at inclusion, after chemotherapy, after radiotherapy and at each follow-up visit, and sent to the Uppsala Regional Oncological Centre, where incoming data were registered, completed if needed and computerised. Life-table analyses were performed and tested according to Cox and log-rank tests. The Student *t*-test was performed for comparison between groups. The Fisher's exact test was used to compare groups with respect to local control and metastases. Multivariate Cox analysis was performed with respect to treatment and to certain factors of probable prognostic importance.

RESULTS

Inclusion

After 5 years, the inclusion rate had decreased and the study was ended in May 1989, by which time 327 patients had been enrolled, 164 randomised to the radiotherapy arm and 163 to the combined treatment arm.

25 (8%) patients were excluded, 10 in the radiotherapy arm and 15 in the combined treatment arm (Table 1). In 19 patients, treatment was never initiated because the exclusion criterion was discovered shortly after randomisation or the patient denied participation. No further information was received for these patients except whether they survived, which was gained from the Swedish population register. An analysis of the survival of all 327 randomised patients was performed. In 6 patients, the histological diagnosis was changed at autopsy.

Of the 302 remaining patients, 154 were allocated to radiotherapy only and 148 to chemotherapy followed by radiotherapy.

Population details

Of the 302 remaining patients, there were 253 (84%) men and 49 (16%) women and the median age was 64 years. There were no significant differences between the two treatment groups with respect to age, gender, tumour stage, performance status, presence of supraclavicular metastases or thoracotomy without resection (Table 2).

Table 1. Reasons for excluding cases from the analysis

Reason	Radiotherapy only	Combined treatment
Diagnosis changed, mainly at autopsy	3	3
Patient non-participation	1	4
Insufficient respiratory capacity	1	2
Distant metastases found before start of treatment	1	3
Insufficient renal function for cisplatin treatment	0	1
Other violations of inclusion criteria, mainly poor general condition	4	2

In exclusion with respect to changed diagnosis, the exclusion was late, but in the other, patient exclusion was early, before treatment was started.

Table 2. Patient characteristics

Parameters	Number of patients	
	Radiotherapy	Combined treatment
Randomised	164	163
Excluded	10	15
Included	154	148
Men	131	122
Women	23	26
Median age (years)	64	64
Age		
<50	8	9
50–60	33	30
61–70	79	75
>70	34	34
Performance status		
Zubrod		
0	68	61
1	68	60
2	4	18
3	3	6
Unclassified	1	3
Supraclavicular nodes	5 (3%)	7 (5%)
Thoracotomy	26 (17%)	29 (20%)
Stage		
I	27	17
II	10	4
IIIA	98	102
IIIB	8	10
Unclassified	11	15
T1	11	5
T2	92	90
T3	47	44
T4	3	6
TX	1	3
N0	56	34
N1	14	10
N2	69	87
N3	5	4
NX	10	13

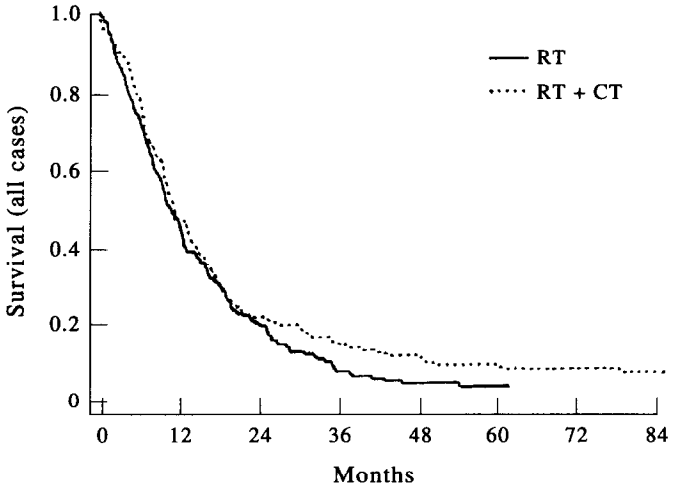

Figure 1. Survival of patients receiving radiotherapy only or combined treatment, including all patients. Log-rank test demonstrates a trend to improved survival in the chemotherapy group ($P = 0.11$). RT, radiotherapy; CT, chemotherapy.

Tumour stages

Staging was accomplished in 143 cases (93%) in the radiotherapy only arm and in 133 cases (90%) in the combined treatment arm. Of the patients staged, 74% in the radiotherapy only arm and 84% in the combined treatment arm had stage III disease, and the remaining cases had stage I or II disease (Table 2). No difference was found between the treatment arms with respect to thoracotomy and supraclavicular nodes (Table 2).

Treatment compliance

In the radiotherapy arm, 114 patients received the planned irradiation dose (74%). 4 patients (3%) received a higher dose than planned (58 Gy or more), 28 (18%) a lower dose (54 Gy or less) and 8 (5%) no irradiation at all. In the combined treatment arm, 93 (63%) patients received the planned irradiation dose, 8(5%) a higher dose, 23 (16%) a lower dose and 24 (16%) patients no irradiation at all.

Early death, deterioration in general condition or the development of metastases were the primary reasons for dose reductions. Three chemotherapy courses were given to 85 patients (57%), two courses to 28 patients (19%), one course to 26 patients (18%) and no drugs at all to 9 patients (6%). The reason why less than the planned two courses were given was mainly because of PD, treatment toxicity or deterioration in general condition. Thus of 444 (148×3) possible chemotherapy courses, 337 (76%) were given.

Survival and response

Survival of all 327 randomised patients demonstrated a trend towards improved survival in the combined treatment group ($P = 0.16$). A similar trend was found after exclusion of patients according to Table 1 ($P = 0.11$) (Figure 1). Median survival was 10.5 months in the radiotherapy arm and 11 months in the combined treatment arm. Survival at 2 years was 17% in the radiotherapy group and 21% in the combined treatment group. At 5 years, it was 1.4% and 3%, respectively. The multivariate Cox analysis demonstrated a favourable effect on survival by the addition of chemotherapy (relative risk (RR) = 0.78; $P = 0.045$) (Table 3).

No patient surviving for 5 years, 2 in the radiotherapy arm and 4 in the combined treatment arm, had any evidence of tumour disease. One patient in the combined treatment arm died after 5 years from heart and lung insufficiency, but 5 patients, of which 3/253 were men (1%) and 2/49 (4%) were women were still alive more than 6 years after treatment. Gender had no significant impact on survival. Tumour stage had no influence on survival according to lifetable analysis (Figure 2). However, Cox analysis indicated an increased RR for early death in patients with stage IIIA disease (RR= 1.31; $P = 0.146$) compared with stage I disease. RR was still higher and significant for the 18 patients with stage IIIB disease (RR 1.86; $P = 0.042$) (Table 3). Survival was worse in patients with a worse performance status according to life table analysis ($P = 0.02$) (Figure 3) and to Cox analysis with respect to Zubrod group 2 compared with group 0 ($P = 0.04$) (Table 3).

Response evaluation according to chest X-ray was possible in 270 patients.

Table 3. The importance of stage, performance status, age and treatment according to Cox analysis

	Risk ratio	*P* value
Tumour stage		
Stage I	1.0	–
Stage II	1.27	0.482
Stage IIIA	1.31	0.146
Stage IIIB	1.86	*0.042*
Performance status (Zubrod)		
0	1.0	–
1	1.09	0.506
2	1.57	*0.040*
3	2.16	0.080
Age (years)		
<70	1.0	–
⩾70	1.10	0.339
Treatment		
Radiotherapy	1.0	–
Chemotherapy	0.78	*0.045*

Those *P* values shown in italic are significant.

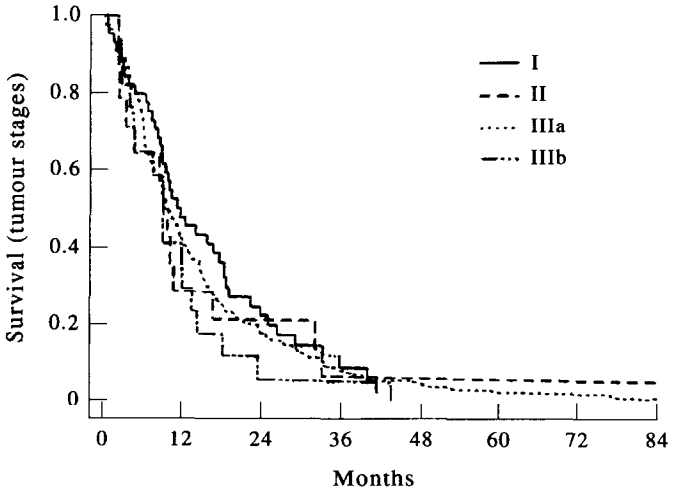

Figure 2. Survival of patients at different tumour stages.

In the remaining 32 patients, the X-ray images had been destroyed or were impossible to evaluate. At evaluation, 'no response (SD)' and 'PD' were not separated.

A CR according to X-ray images was obtained in 22/270 patients (8%), 9/137 (7%) in the radiotherapy arm and 12/133 (9.0%) in the combined treatment arm. In 14/22 patients (64%) with CR, local control (sterilisation of the primary tumour, see Patients and Methods) was achieved; 4/14 were still alive with no evidence of disease (NED) more than 5 years after randomisation, 5 were free from tumour at autopsy and 5 were considered free from tumour according to chest X-rays and survival for more than 4 years without symptoms of lung tumour. 3 of these patients belonged to the radiotherapy arm and 11 to the combined treatment arm.

A PR was achieved in 63/270 patients (23%), 32/137 (23%) in the radiotherapy arm and 31/133 (23%) in the combined treatment arm. In 4/63 (6%) of these patients, local control was achieved, and 1 patient is alive with NED and 3 were free from tumour at autopsy. 2 cases were randomised to the radiotherapy arm and 2 to be combined treatment arm. The remaining 185/270 patients (69%) were judged as having SD or no response, although in 2/185 (1%) local control had been achieved according to autopsy. Of the 32 patients unevaluable with respect to response, 1 patient achieved local control according to autopsy. Local control was found in only 21 patients (8%). In the radiotherapy group, 7/154 (5%) and in the combined treatment group 14/145 (10%) achieved local control ($P = 0.08$).

The presence of metastases was possible to evaluate in 258 patients. 92/258 (36%) evaluable patients were free from distant metastases according to follow-up or autopsy, 42/133 (32%) in the radiotherapy group and 50/125 (40%) in the combined treatment arm ($P = 0.10$).

Cure (sterilisation of the primary tumour and no metastases, see Patients and Methods) was achieved in 14/302 (5%) of the patients, 4/154 (3%) in the radiotherapy group and 10/148 (7%) in the combined treatment arm ($P = 0.07$). Of these 14 patients, 5 were alive with NED more than 5 years after treatment. Of the 9 deceased patients, 7 belonged to the combined treatment arm and 2 to the radiotherapy group. In 8 of these patients, autopsies verified that they were free from lung cancer. The ninth patient was tumour free for 4.5 years, but then deteriorated due to acute myeloid leukaemia and died within a few

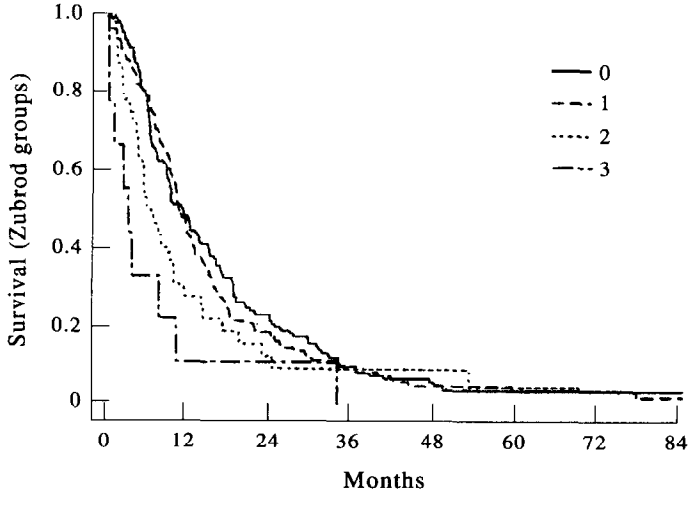

Figure 3. Survival of different performance status groups (Zubrod 0, 1, 2 and 3).

Table 4. Treatment toxicity

	Number of patients	
	Radiotherapy only	Combined treatment
Ototoxicity	0	12
Nephrotoxicity	0	8
Septicaemia	0	5 (2 lethal)
Neuropathy	0	1
Emesis	0	8
Pneumonitis	11	10

World Health Organisation toxicity grade II–IV is presented in the table. With respect to emesis, patients refusing further treatment with drugs are given.

months without evidence of lung cancer, according to a chest X-ray.

Treatment toxicity

Irradiation induced pneumonitis in 11 patients in the radiotherapy arm and in 10 patients in the combined treatment arm, corresponding to a total frequency of 7%, with no significant difference between the treatment groups. No patients died from pneumonitis (Table 4).

In the combined treatment group, leucopenia with septicaemia were registered in 5 patients, of which 2 were lethal. One patient had an anaphylactic reaction to cisplatin. 8 patients (5%) received less chemotherapy than planned, rejecting treatment, mainly because of sickness. 2 patients in the combined treatment group (1%) developed leukaemia (acute and chronic myeloid) after 4 and 5 years, respectively. One of these patients was considered free from lung cancer as mentioned above. No leukaemia was found in the radiotherapy only group.

9/14 cured patients (64%) died within 6 years of the start of treatment, 7/10 in the combined treatment group and 2/4 in the radiotherapy only group. 5 of these patients died from heart disease.

Autopsy

Autopsy was performed in 122 cases (40%), 60 in the radiotherapy arm and 62 in the combined treatment arm. Reasons for omitting autopsy were mainly that the patient had obvious tumour progression or that relatives of the patient objected to the procedure.

DISCUSSION

This is the second largest reported study evaluating the use of chemotherapy added to radiotherapy in patients with locally advanced NSCLC. It included, however, some patients with stage I and II tumours. These patients should, as a rule be treated with surgery, but some of these patients were inappropriate candidates for surgery because of limited heart or lung capacity and others refused it. There might also be a risk that the data on which the TNM classification was based were incomplete, leading to understaging. However, tumour stage was still a prognostic factor according to multivariate analysis, in concordance with an earlier report [14].

In this study, 8% of randomised patients were excluded, the majority shortly after randomisation and before the start of treatment, because of the detection of an exclusion criterion. The main risk with exclusion is selection bias, and although there were a few more patients excluded in the combined treatment arm, there were still numerically more patients with poor prognostic characteristics, worse Zubrod stages and higher tumour stages in this group. However, to account for any bias, survival data for the excluded patients were obtained from the Swedish population register and an analysis of the survival of all randomised patients was performed. This demonstrated a similar trend to improved survival in the combined treatment group as that found in the analysis in which patients were excluded.

Several large [15–19] and smaller [20–22] randomised studies have investigated the same problem with different results. In an Italian study, the treatment arms were almost identical to those in our study: 56 Gy for the primary

Table 5. Comparison of five large randomised studies

Study [Ref.]	Finnish [15]	CALGB [16]	French [17, 18]	NCCTG [19]	Swedish [current]
Numbers in study	119/119	77/78	177/176	58/56	154/148
Median survival (months)	10.3/11.0	9.7/13.8	10/12	10.3/10.4	10.5/11
Survival rate					
1 year (%)	41/42	40/55	41/50	45/46	42/45
2 years (%)	17/19	13/26	14/21	16/21	17/21
3 years (%)	—	11/23	5/11	—	6/13
5 years (%)	—	—	—	7/5	1.4/3
CR (%)	11/15	19/16	29/16	17/14	6/8
PR (%)	39/49	7/19	15/15	14/11	21/21
Local control (%)	—	10/22	15/17	—	5/10
Distant metastases (%)	—	53/52	38/26	—	68/60
Lethal toxicity (%)	—	0/0	3/5	0/2	0/2

Numbers shown are for radiotherapy only/radiotherapy + chemotherapy. CR, complete response; PR, partial response; CALGB, Cancer and Leukaemia Group B; NCCTG, North Central Cancer Treatment Group.

tumour or two courses of cisplatin, 100 mg/m^2, and etoposide, 120 mg/m^2, followed by 56 Gy. In spite of a small number of patients (56), a borderline survival improvement was found ($P = 0.06$) [19].

The four largest studies are compared with our study in Table 5. Two of these [16, 18] demonstrated a survival advantage with chemotherapy and two did not [15, 19]. The choice of drugs, doses, patient selection and sample sizes have been suggested as possible explanations for these differences [23–26].

The importance of including cisplatin at a sufficient dose has been pointed out [23]. In one of the studies with no survival advantage with chemotherapy, cisplatin was not used [19] and in the other only a low dose (40 mg/m^2) was applied [15]. In our study, and in the studies with a strong trend or a significant survival advantage, high-dose cisplatin has been used [16–18, 20].

The 1-year survival rate was 40–45% for the radiotherapy arm and 45–55% for the combined treatment arm, and the 2-year survival rate was 13–17% and 21–26%, respectively (Table 5). Long-term survival was thus poor, and it has been questioned if treatment is in fact worthwhile. In a study from Scotland and Denmark, a three-armed study compared no initial antitumoural treatment with radiotherapy (50 Gy) or combined treatment two courses of cisplatin, 100 mg/m^2, and vindesin, 3 mg/m^2 followed by 50 Gy [26]. Palliative radiation was given to patients without initial treatment, when symptoms developed. In this study, the 1-year survival rate was 34, 52 and 53 weeks, for no treatment, radiotherapy only and combined treatment, respectively. The 2-year survival rate was 15, 20 and 20%, respectively. The 2-year survival rate without treatment in this study was comparable to the 2-year survival with radiotherapy only in the randomised studies (Table 5). No responses were, as might be suspected, found in the non-treated patients and there was a trend towards an impaired survival in these patients. However, as the authors noted, the small number of patients, only 39 in each arm, precluded robust statistical analysis [22].

A meta-analysis in progress [27] has indicated a survival advantage with the addition of chemotherapy to radiotherapy, but that improvement is limited, in accordance with the results of the present study.

A poor local control was the greatest obstacle to long-term survival in this and other studies [16–18]. Local control has been defined differently, from sterilisation of the entire tumour to the lack PD. CR according to chest X-rays was not a reliable measurement of tumour sterilisation. 8/22 (36%) of patients with CR failed locally and 6/21 (29%) of the patients with local control did not have a CR according to X-rays.

The low rate of sterilisation of the primary tumour demonstrated in our study might be partly explained by the fairly high autopsy rate that disclosed viable primary tumours in patients judged as having CR and PR according to radiography. A local failure rate identical to that of the radiotherapy arm of our study, 95%, was found after radiotherapy in a British study with a 69% rate of autopsies [28].

In our study and also in one of the other large studies, the addition of chemotherapy achieved a trend towards better local control [15]. This was not the case in the French study, but they found a significantly decreased rate of metastic disease in the combined treatment arm [17, 18]. In our study, a trend towards a decreased metastatic rate was demonstrated.

The use of a split course in the radiotherapy arm of our study might be an explanation for the poor local control, as there are data indicating that prolonged total treatment time impairs local control rate [29]. Another method improving the local effect is to give chemotherapy concomitantly with radiation. In a German study, radiation was given concurrently with weekly cisplatin [21]. This study demonstrated a better survival by adding preradiation chemotherapy. In an EORTC study, daily cisplatin was still more effective than weekly cisplatin [30]. A further improvement in local control might be to use accelerated hyperfractionated irradiation [31].

Toxicity reduced the favourable effect of chemotherapy, with early deaths caused by the chemotherapy. In addition, leukaemia which developed after a few years in 2 patients from the combined treatment group (none developed in the radiotherapy group) might have been drug induced. An increased risk of acute non-lymphocytic leukaemia has been associated with etoposide [32]. The death of 9/14 cured patients within 5 years, 1 from leukaemia, the others from non-malignant lung and particularly heart disease, might indicate late heart and lung toxicity from treatment. It seems important in the future to search for better treatment to consider particularly heart toxicity.

In conclusion the addition of chemotherapy to radiation achieved a reduced RR for early death, but with a very modest life-prolonging effect. The major problem of the present treatment was an insufficient effect on the primary tumour, with local failure in more than 90% of patients. Another problem was metastatic disease, which was found in 60–70% of the patients. A third problem was treatment toxicity, decreasing the benefits of adding chemotherapy. Although the survival advantage with the chemotherapy used in this study was small, our intention is to use combined treatment as the control arm in further studies of this disease.

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APPENDIX

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