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Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus

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Abstract

Between 1983 and 1989, 211 patients with inoperable squamous cell carcinoma of the oesophagus were randomised in a study comparing split-course irradiation (two courses of 20 Gy in five fractions of 4 Gy, separated by a rest of 2 weeks) (arm A) and the same split-course irradiation in combination with cisplatin (CDDP) (3–4 days before each of the two courses of radiotherapy, repeated every 3–4 weeks, for a total of six cycles) (arm B). The Cox's regression model with retrospective stratification was used to compare the two arms to correct for the imbalance at randomisation of the T classification. The median overall survival was 7.9 (95% confidence interval (CI) 7.3–9.4) months in arm A and 9.6 (95% CI 8–13.5) months in arm B. The difference in overall survival was only borderline significant ($P=0.048$) with a reduction of the instantaneous rate of death of 24%. The 1 and 2 year overall survival rate were respectively 29% (95% CI 21–37%) and 15% (95% CI 8–22%) in arm A and 45% (95% CI 36–54%) and 20% (95% CI 13–27%) in arm B; thereafter, the survival curves became similar. The median progression free survival (PFS) was 5.0 (95% CI 4.6–5.7) versus 6.9 (95% CI 5.3–8.7) months ($P=0.028$) and the median time to local progression was 6.2 (95% CI 5.1–7.6) months versus 10.9 (95% CI 8.1–15.5) months ($P=0.018$), respectively, in arms A and B. Haematological toxicities were slightly more commonly observed in the combined group (1% versus 6%). This study shows that split-course irradiation in combination with CDDP is very well tolerated and should be preferred to radiotherapy alone.

Keywords: Oesophageal cancer; Squamous cell carcinoma; Split-course irradiation; Cisplatin; Chemotherapy

1. Introduction

The prognosis of patients with oesophageal cancer is poor, even after a curative resection. Most of the patients die from distant metastases which indicates that from the first clinical symptoms of the disease it is systemic in most of the patients. This fact ensures strong support for combined treatment modalities that expect to have a maximal local effect and to eradicate distant micrometastases in order to improve survival. The Gastro Intestinal Tract Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) initiated in 1983 a phase III controlled clinical trial of irradiation versus irradiation and cisplatin (CDDP) in patients with irresectable squamous cell carcinoma of the oesophagus (EORTC 40831). In the early eighties, results from phase II trials showed that CDDP and bleomycin were among the most active drugs against oesophageal carcinomas. The group chose to test CDDP as a single agent in combination with irradiation because of the risk of pulmonary toxicity associated with the use of bleomycin which might be aggravated with concomitant mediastinal irradiation and because there was no clear demonstration of a

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benefit with polychemotherapy. At that time, the total dose of irradiation was given on an inpatient basis due to the poor tolerance by the majority of the patients. An admission of more than 5 weeks was considered to be too long for patients with an expected short survival. To prevent a long hospital stay, it was therefore decided to introduce a split-course scheme, a method which was described for patients with bronchogenic carcinoma [1], head and neck cancer [2] and in the early seventies for oesophagus carcinoma [3].

2. Patients and methods

2.1. Patients

All patients were required to have squamous cell carcinoma, be aged under 70 years, have had no prior chemotherapy, a performance status of World Health Organization (WHO) 0–2; any T1–3 lesion according to the 1979 International Union Against Cancer (UICC) classification (T1: tumour $\leqslant 5$ cm, T2: tumour > 5 cm, T3: extra oesophageal spread), but without superficial (cervical) lymph node metastases or distant metastases (infradiaphragmatic lymph node involvement was not a reason for exclusion because at the beginning of this study we considered that, with the usual available techniques, there might be doubt on the diagnosis of such lesions). Any patient considered as inoperable because of local general physical condition or who refused surgery, but fulfilled these criteria was eligible.

Exclusion criteria at entry were: a weight loss $> 20\%$ of the usual weight; an extension of the tumour to the pharyngeal or gastric junction; a tracheal or bronchal involvement, (compression was not a criteria for ineligibility); evidence of distant visceral metastasis or supraclavicular lymph nodes; no previous malignancy except basal cell carcinoma of the skin; clinical or biological criteria which prevented chemotherapy treatment, i.e. serum creatinine > 100 μmol/l, polymorphonuclear cell-count $< 2.0 \times 10^9$/l or platelet count $< 80 \times 10^9$/l; concomitant cardiac failure requiring diuretics.

2.2. Chemotherapy and radiotherapy

The patients were randomised to radiotherapy alone (arm A) or CDDP combined with radiotherapy (arm B).

Arm A consisted of treatment with radiotherapy alone given in two courses of 20 Gy in five fractions of 4 Gy within 5 days with a rest-interval of 2 weeks between the two courses. The given dose was considered equivalent to 55–60 Gy delivered in a classical fractionated protocol. The target-volume included the oesophageal tumour site, plus 2 cm laterally and 5 cm above and below the tumour edges and was limited to 0.5–1 cm beyond the anterior face of the vertebras on X-ray films. Supraclavicular and/or infradiaphragmatic regions were not included in the target volume.

Any technique which was able to deliver 100% of the prescribed dose to the target volume was allowed. Four oblique fields opposed 2 by 2 (X technique) or 3 fields: 1 posterior and 2 oblique posterior (inverted Y technique) were recommended. The dose on the spinal cord had to be less than 30 Gy (i.e. 75% of the reference dose).

Arm B combined the same radiotherapy protocol with CDDP, given 3 or 4 days before each radiotherapy course and then every 3 or 4 weeks until a total of six cycles were given. CDDP was administered at a dose of 100 mg/m^2 in 500 ml of an 10% mannitol solution as an intravenous (i.v.) drip over 30 min. The schedule included prehydration with 2 l of a 5% glucose solution infused within 4 h and a posthydration with 2 l of a 5% glucose solution over 6 h. Treatment was delayed until restoration if the serum creatinine level was > 110 μmol/l or platelet count $< 80 \times 10^9$/l or white blood cell (WBC) count $< 2.0 \times 10^9$/l. Chemotherapy was stopped if there was no normalisation after 4 weeks.

2.3. Criteria for evaluation

The main criteria used to evaluate the efficacy of the treatments were overall survival (OS), progression-free survival (PFS), time to local progression and time to local or distant progression. Overall survival was defined as the time interval between the date of randomisation and the date of death and PFS between the date of randomisation and the date of local or distant progression or death whichever occurs first. The time to local or distant progression was considered from randomisation to progression (local or distant) and the time to local progression from randomisation to local progression only. Development of lymph node metastases and/or distant metastases were considered as failures. Local progression was documented by barium X-ray and endoscopy, histologically proven or not.

2.4. Follow-up

The visits of the patients were planned on the 2nd and the 4th months after the start of the treatment, then every 3rd month until 18 months, and finally every 6th month until death. The following parameters were required from the second month after start of treatment: physical examination including performance status and nutritional status assessment, blood cell count and chemistry, chest X-ray, barium X-ray of the oesophagus or endoscopy.

2.5. Statistical considerations

The trial was originally designed to detect an increase in the median survival from 9 months in the radiotherapy

arm to 12 months in the combination arm with a power of 80% and a one-sided tail test at a significance level of 5%.

It was estimated that a total 400 patients (200 in each treatment arm) recruited during 2 years and followed for a minimum of 1 year would provide sufficient power. After assessment for the inclusion criteria, patients were randomised by the EORTC Data Center in Brussels. Stratification was performed by institution and weight loss in relation to the usual body weight ($\leqslant 10\%$ versus $>10\%$).

The descriptive report, characteristics at entry and toxicities, were based on all eligible patients. Toxicities were reported according to the treatment the patient received. Treatment comparisons for efficacy were performed for all randomised patients according to an intent-to-treat policy (all randomised patients were used in the analyses and according to the arm in which they were randomised). For information purposes, the treatment comparisons were also performed on the eligible patients only.

Time-to-event end-points were estimated using the Kaplan–Meier technique [4]. For all these endpoints, if the event was not observed the patient was censored at the last time he was traced. Differences in the time to events were initially compared using a two-sided unstratified Log-rank test [5]. To correct for an inbalance in the distribution of the patients for important prognostic factors in the treatment arms, such as the clinical stage at entry, it was decided to use a Cox's proportional hazards regression model with a retrospective stratification for the T classification [6].

3. Results

From December 1983 to February 1989, 221 patients from 11 institutions were randomised (Fig. 1). Then it was decided to close the trial because of the low accrual rate. There were 111 patients in the radiotherapy arm (A) and 110 in the radiotherapy + CDDP arm (B). All patients were evaluated and 18 (8%) were considered ineligible (10 in A and 8 in B). The reasons for ineligibility were inadequate staging (15), poor physical condition (2) and prior treatment (1).

Except for clinical stage at entry, the characteristics of the patients showed no differences in the distribution of the patients between the treatment groups in terms of age, gender, performance status or weight loss (Table 1). There were no important differences in the lesion characteristics according to the length of the tumour, bifocality, differentiation of the tumour and nutritional

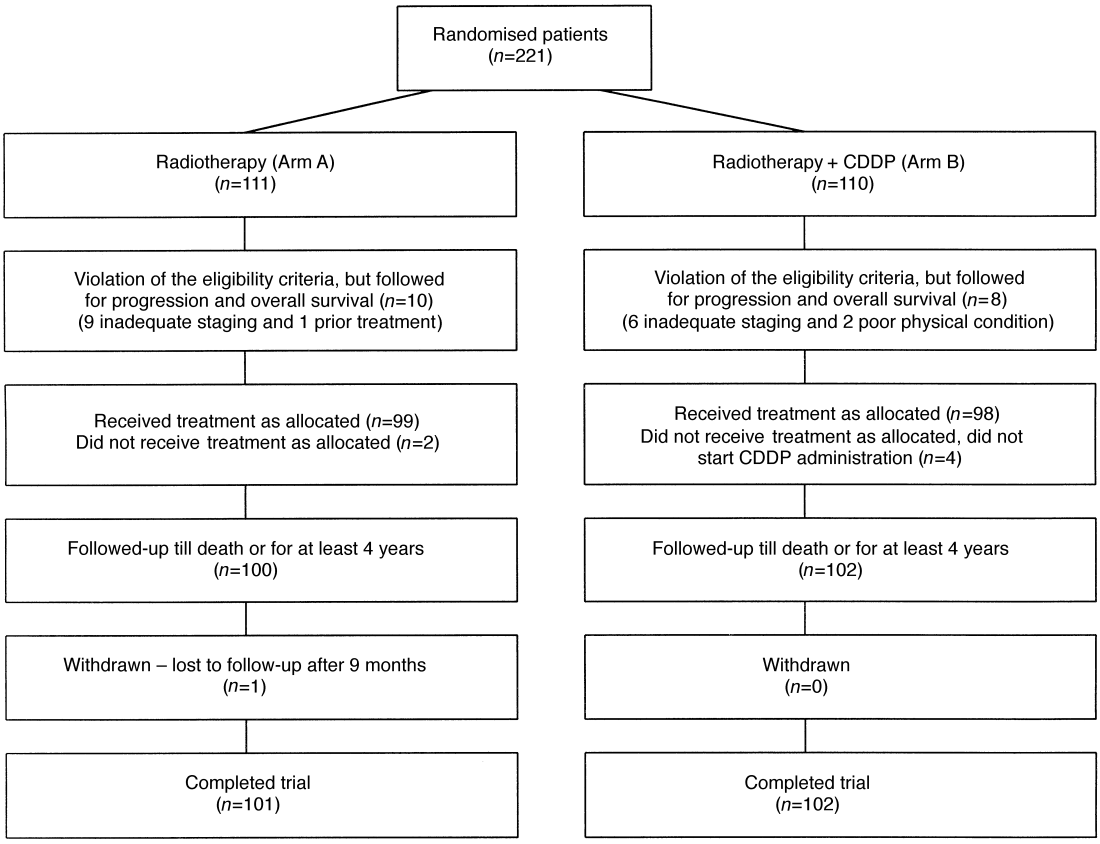

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639).

status. Only 12 patients, in each group, were not able to intake food orally, while 3 had a catheter enterostomy. 6 patients were considered eligible in spite of a positive echography of the coeliac lymph nodes.

2 patients did not receive the allocated treatment because of early progression and 2 patients in each treatment arm received the opposite treatment owing to institutional decisions. In the treatment analysis, these 4 patients were considered in the treatment arm in which they were randomised initially, however, in the evaluation of the side-effects and toxicity they were analysed as they were treated. In arm A, 92% (93/101) and in arm B 93% (95/102) of the patients did receive the planned two courses of radiotherapy. The median number of courses of CDDP in patients randomised in arm B was four (range 0–8), while 44% (43/98) of the patients received at least six cycles. Of the patients who stopped earlier in 51% (28 patients) the reason was progression of disease, in 17 patients (30%) excessive toxicity and in 5 patients (10%) the refusion of ongoing treatment. In arm B, 4 patients did not start CDDP treatment, 2 because of early progression and 2 received radiotherapy only by institutional choice.

Table 1
Patient characteristics at randomisation by treatment arm (eligible patients, $n=101$ in R and 102 in RC)

Characteristics	Radiotherapy (R) *n* (%)	Radiotherapy +CDDP (RC) *n* (%)
Age (years)		
Median (range)	61 (44–75)	62 (40–75)
Sex		
Female	5 (5)	2 (2)
Male	96 (95)	100 (98)
Performance status (WHO)		
0	19 (19)	22 (22)
1	50 (50)	52 (51)
2	24 (24)	18 (18)
3	0	1 (1)
Unknown	8 (8)	9 (9)
Weight loss (%)		
$\leqslant 10$	70 (69)	72 (71)
>10	31 (31)	30 (29)
Histopathology		
Well differentiated	55 (54)	49 (48)
Poorly differentiated	29 (29)	28 (27)
Undifferentiated	2 (2)	5 (5)
Unspecified	9 (9)	11 (11)
Unknown	6 (6)	9 (9)
T category		
T1	21 (21)	12 (12)
T2	66 (65)	70 (69)
T3	13 (13)	20 (20)
Unknown	1 (1)	0
N category		
N0	69 (68)	68 (67)
N1	4 (4)	3 (3)
N2	1 (1)	1 (1)
N3	1 (1)	0
NX	26 (26)	30 (29)
M category		
M0	97 (96)	100 (98)
M1	4 (4)	2 (2)

The irradiation given in a split-course manner was very well tolerated. In the radiotherapy-alone arm (A), only 1% haematological toxicity was observed and no WHO grade 3 and 4 toxicity was reported for nausea/vomiting, diarrhoea, and respiratory, skin, mucosae and fever toxicities. In the combined treatment arm (B), 6% haematological 3–4 toxicity was observed, 3% renal toxicity and 1% auditory toxicity. 3% of the patients suffered oesophagitis. Nausea and vomiting (WHO grade $\geqslant 3$) was seen in 12% of the patients of this group, despite the use of antiemetics. No cardiac, respiratory or neurological toxicity was encountered in any of the two treatment arms (Table 2).

3.1. Survival analysis

An inbalance was observed in the clinical stage at entry, ie there were less patients in the T_1 category and more in the T_3 category in the experimental arm than in the control arm. As a consequence, this important prognostic factor had a favourable impact on survival for the control arm. Therefore, in addition to the unstratified Log-rank test, we also quantified the difference between the treatment, considering a retrospective stratification for the clinical stage. This avoids the dilution of the treatment effect that occurs because of this inbalance.

Except for 1 patient lost to follow-up after 9 months in arm A, all patients were followed untill death (102/111 in arm A and 104/110 in arm B) for more than 4 years. The main cause of death was malignancy with local or distant progression. Based on an intent-to-treat analysis, the different time-to-event endpoints are reported in Table 3. The median overall survival and the 95% confidence interval (CI) was 7.9 (CI 7.3–9.4) months in arm A and 9.6 (CI 8–13.5) months in arm B. The median PFS was 5.0 (CI 4.6–5.7) versus 6.9 (CI 5.3–8.7) months and the median time to local progression was 6.2 (CI 5.1–7.6) versus 10.9 (CI 8.1–15.5) months in arms A and B, respectively. The unstratified Log-rank test ignoring the possible bias introduced by the imbalance at entry for clinical stage showed no significant difference for overall survival ($P=0.173$), a borderline significant difference in favour of the combination arm (B) for PFS ($P=0.067$) and a significant difference in favour of the combination arm (B) for time to local progression ($P=0.023$) and time to progression ($P=0.042$).

Considering the retrospective stratification for clinical stage at entry, the difference is borderline significant for overall survival ($P=0.048$) and significant with respect

Table 2
Toxicity and side-effects according to the World Health Organization (WHO) scale (eligible patients who started their treatment, $n=101$ in R and 100 in RC)

	Radiotherapy (R) *n* (%)	Radiotherapy +CDDP (RC) *n* (%)
Haematological toxicity		
Haemoglobin		
0	81 (80)	46 (46)
1	2 (2)	28 (28)
2	0	22 (22)
3	0	3 (3)
Unknown	18 (18)	1 (1)
WBC		
0	80 (79)	46 (46)
1	2 (2)	28 (28)
2	0	21 (21)
3	0	4 (4)
4	1 (1)	0
Unknown	18 (18)	1 (1)
Platelets		
0	84 (83)	93 (93)
1	0	4 (4)
2	0	2 (2)
Unknown	17 (17)	1 (1)
Any haematological toxicity		
0	79 (78)	27 (27)
1	4 (4)	33 (33)
2	0	33 (33)
3	0	6 (6)
4	1 (1)	0
Unknown	17 (17)	1 (1)
Non-haematological toxicity		
Bilirubin	Not documented	
0		90 (90)
1		3 (3)
Unknown		7 (7)
Urea	Not documented	
0		85 (85)
1		10 (10)
Unknown		5 (5)
Creatinine	Not documented	
0		87 (87)
1		8 (8)
2		1 (1)
Unknown		4 (4)
Nausea/vomiting		
0	81 (80)	49 (49)
1	3 (3)	26 (26)
2	0	12 (12)
3	0	11 (11)
4	0	1 (1)
Unknown	17 (17)	1 (1)
Anorexia	Not documented	
0		63 (63)
1		19 (19)
2		11 (11)
3		2 (2)
Unknown		5 (5)
Renal	Not documented	
0		87 (87)
1		4 (4)
2		4 (4)
3		3 (3)
Unknown		2 (2)

WBC, white blood cells.

to PFS ($P=0.028$), time to local progression ($P=0.018$) and to time to progression ($P=0.031$). The combination of radiotherapy and CDDP reduced the instantaneous rate of death by 24% and the instantaneous rate of local progression by 33%.

In each treatment arm, 24% of the patients who had local progression had simultaneous distant metastases, 18 in arm A and 16 in arm B. 10% of the patients of arm A and 12% in arm B had distant progression without local recurrence.

The overall survival, the time to first progression and the time to local progression curves for all randomised patients are presented in Figs. 2–4, respectively. The 1 and 2 year overall survival were respectively 29% (CI 21–37%) and 15% (CI 8–22%) in the radiotherapy arm (A) and 45% (CI 36–54%) and 20% (CI 13–27%) in the CDDP–radiotherapy arm (B), and thereafter the survival curves became similar. The 1 and 2 year PFS

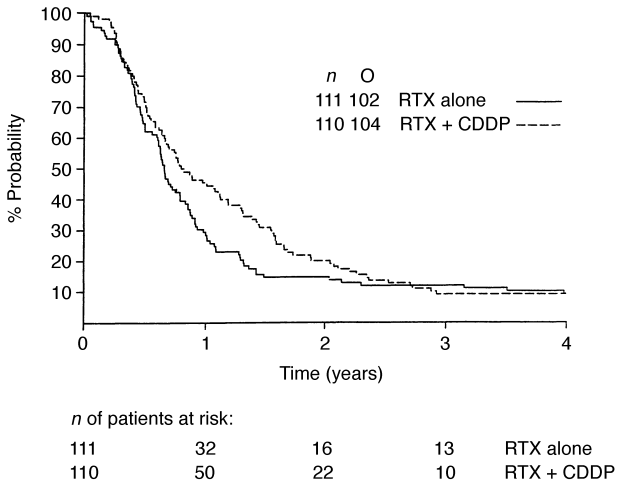

Fig. 2. Overall survival (O = observed number of events and n = number of patients at risk at time 0).

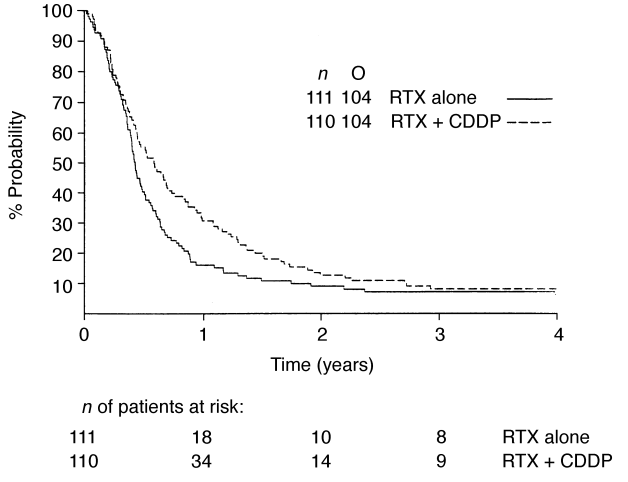

Fig. 3. Time to first progression (O = observed number of events and n = number of patients at risk at time 0).

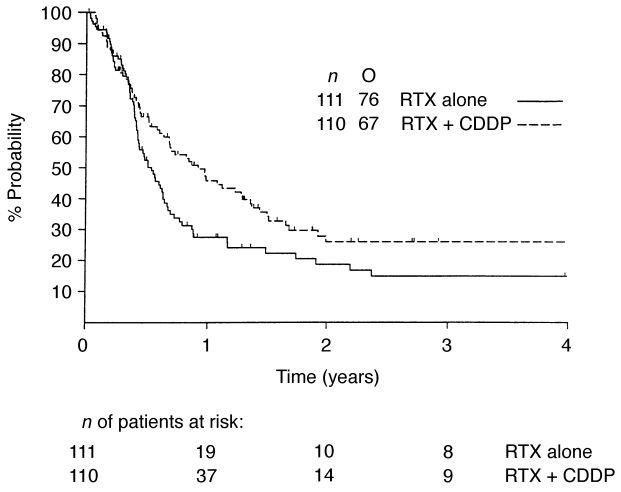

Fig. 4. Time to local progression (O = observed number of events and n = number of patients at risk at time 0).

(95% CI) were respectively 16% (CI 9–23%) and 9% (CI 4–14%) in the radiotherapy arm (A) and 31% (CI 22–40%) and 13% (CI 6–19%) in the CDDP–radiotherapy arm (B); thereafter, the curves again became similar. Approximately 9% of the patients lived longer than 4 years.

All these results were more significant when we restricted the analyses to the eligible patients only (Table 4).

For all patients as well as for those that were eligible, only weight loss and T-classification remained important prognostic factors. A weight loss of more than 10% or a worse clinical stage significantly decreased the overall survival.

4. Discussion

CDDP is a common component of combination chemotherapy for squamous cell carcinoma of the oesophagus, although it is not known whether CDDP is really an essential component of combination chemotherapy for oesophageal cancer [7,8]. CDDP-containing combinations may, however, give a response rate of almost 50%. In these combinations toxic effects are considerable, and although tolerable, these effects may have a very negative effect on the remaining months of the patient's life. CDDP as a single agent is not generally used. In small series, the response rate is 24% or even higher, but in larger, randomised studies, the response rate is less than 20% [7–10]. The same holds true for a local treatment such as radiotherapy, when combined or not with chemotherapy.

There are only few studies investigating the combined effect of CDDP and radiotherapy, although it is well known from animal studies that there is a synergistic effect of the combination [11,12]. In a phase II study, Kolarić and colleagues found a response rate of 56% in locoregionally advanced squamous cell carcinomas [13].

For this study, a split course irradiation schedule was chosen in an attempt to optimise the effect of irradiation and with a high fraction dose (4 Gy) over 5 days in order to decrease the burden to the patient. The theoretical advantage is that the patients may recover during the rest period and that the remaining tumour would become more susceptible to radiation damage due to reoxygenation [2]. The combination of radiotherapy in split courses and CDDP as it was given in this protocol with a free interval of 2 weeks was generally well tolerated, without severe side-effects and deaths due to treatment. Particularly in the radiotherapy alone group,

Table 3
Time-to-event comparisons: all patients, n = 111 in radiotherapy alone (R) and n = 110 in radiotherapy + CDDP (RC)

End-point	No. of events	Median time (95% CI) (months)	Unstratified HR (95% CI)	Unstratified Log-rank P value	Cox's Reg. M. Strat. for clinical stage HR (95% CI)	Cox's Reg. M. Strat. for clinical stage P value
Overall survival						
R[a]	102	7.9 (7.3–9.4)	1.0		1.0	
RC	104	9.6 (8–13.5)	0.83 (0.63–1.09)	0.173	0.76 (0.57–1.0)	0.048
Progression-free survival (PFS)						
R[a]	104	5.0 (4.6–5.7)	1.0		1.0	
RC	104	6.9 (5.3–8.7)	0.78 (0.59–1.02)	0.067	0.73 (0.55–0.97)	0.028
Time to local progression						
R[a]	76	6.2 (5.1–7.6)	1.0		1.0	
RC	67	10.9 (8.1–15.5)	0.68 (0.49–0.95)	0.023	0.67 (0.48–0.93)	0.018
Time to progression						
R[a]	86	5.3 (4.8–6.8)	1.0		1.0	
RC	81	8.1 (6.1–11.7)	0.73 (0.54–0.99)	0.042	0.71 (0.52–0.97)	0.031

CDDP, cisplatin; HR, hazard ratio; CI, confidence interval; Cox's Reg. M. Strat., Cox's Regression Model Stratified for chemical stage.
[a] Reference group.

Table 4
Time-to-event comparisons: eligible patients, $n=101$ in radiotherapy alone (R) and $n=102$ in radiotherapy + CDDP (RC)

End-point	No. of events	Median time (range) (months)	Unstratified HR (95% CI)	Unstratified Log-rank P value	Cox's Reg. M. Strat. for clinical stage HR (95% CI)	Cox's Reg. M. Strat. for clinical stage P value
Overall survival						
R[a]	93	7.8 (6.7–9.5)	1.0		1.0	
RC	96	9.8 (8.2–13.5)	0.81 (0.61–1.08)	0.147	0.7 (0.52–0.93)	0.015
Progression-free survival						
R[a]	95	5.0 (4.5–6.1)	1.0		1.0	
RC	96	7.0 (5.4–8.7)	0.75 (0.57–1.01)	0.055	0.68 (0.5–0.91)	0.009
Time to local progression						
R[a]	72	5.9 (5.1–7.6)	1.0		1.0	
RC	65	10.4 (7.6–15.4)	0.66 (0.47–0.92)	0.016	0.61 (0.43–0.87)	0.005
Time to progression						
R[a]	79	5.4 (4.8–7.1)	1.0		1.0	
RC	77	8.1 (6.1–11.3)	0.72 (0.53–1.0)	0.047	0.67 (0.48–0.92)	0.014

HR, hazard ratio; CI, confidence interval; CDDP, cisplatin; Cox's Reg. M. Strat., Cox's Regression Model Stratified for chemical stage.
[a] Reference group.

no severe side-effects were found. In the combined group, only 6% of the patients had grade 3–4 haematological toxicities and 3% had renal toxicities.

Generally, CDDP alone is very well tolerated as was also shown by Bleiberg and colleagues in a recent study on patients with oesophageal cancer [10]. Thus, the combination of CDDP and irradiation only causes increased haematological toxicities, which is to be expected. The combination with CDDP possibly resulted in a synergistic effect which was needed for local control of the primary tumour. Indicative of this, finding the local effect was significantly better in the combined treatment group. We are not sure whether the split-course irradiation is superior to a closed series of irradiation. In studies on head and neck cancer, the split-course schedules have failed to increase the complete response rate [2]. Thus, the theoretical advantage of split-course irradiation on the tumour itself may not have the expected effect in the patient.

However, what we learnt is that this mode of treatment is very well tolerated and had a good local effect. Although the survival of both groups did not show significant differences, there is a strong suggestion that the combination of CDDP and radiotherapy is more effective than radiotherapy alone. Almost half of the patients (45%) were still alive after the first year in the combination-treatment group, while only approximately 30% were alive in the radiotherapy alone group. This also means that effective local control has a positive influence on survival in some patients, presumably the patients with limited local disease. The eventual effect of improving the PFS without lengthening the overall survival can mainly be attributed to better local control of the disease, which at the same time has a high impact on the quality of life.

Bleiberg and colleagues found a median time to progression of 18 weeks in advanced squamous cell carcinomas of the oesophagus with CDDP alone [10]. The median duration of survival was 28 weeks. In our study, in arm B the median time to first progression in the combined treatment group was 6.9 months (=29.9 weeks) and to first local progression 10.9 months (=47.2 weeks). The median overall survival was 9.6 months (=41.6 weeks). These differences are considerable particularly with respect to local control and may be explained by the synergistic effect of the combination of CDDP and irradiation on the local control.

In the combined treatment arm of our study, the chemotherapy was given sequentially 3–4 days before the irradiation. Recently the long-term follow-up results of the Radiation Therapy Oncology Group (RTOG 85-01) have been published [14]. In that trial, patients were randomised to radiotherapy alone (64 Gy, 6.4 weeks) or concurrent radiotherapy (50 Gy, 5 weeks) and combination chemotherapy (CDDP and 5-fluorouracil). This concurrent chemoradiotherapy resulted in a significantly increased overall survival compared with radiotherapy alone. There were no causes of death 5 years posttreatment. The expected 10 year survival rate in the combined group was even as high as 20%. Although in our study we claim some synergistic effect of the sequential combination, the RTOG 85-01 study proved clearly that concurrent chemoradiotherapy is superior to other regimens, and that the combination of CDDP and 5-fluorouracil has a more systemic effect than CDDP alone.

The effect on survival in our study, which was the primary end-point of the trial, was only significant after adjusting for the imbalance in the T-categories and even then it was of borderline significance. We should also

take into account that the trial was stopped early due to the lack of recruitment of patients. The power of the trial to detect an increase in the median survival of 33% as originally planned with the observed number of deaths is rather low: 53% for a two-sided test [15]. This also implies that other variables such as prognostic factors could not reach significant levels because of the small numbers. The only major prognostic factor which could be evaluated was weight loss before treatment. This confirms the findings regarding weight loss in earlier studies on oesophageal cancer [10,16]. However, the results in this study must be interpreted with caution due to the lack of statistical power as a result of the low rate of accrual. In fact, this will mean that in cases of severe weight loss ($>10\%$), the therapy should be directed more at the local tumour than at general survival. This will give a better quality of life for this patient group. This study demonstrates a clear effect of the combined treatment for local control and we conclude that the use of the combined treatment in this group of patients is to be preferred to radiotherapy alone.

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References

1. Perez CA, Stanley K, Rubin P, *et al*. A prospective randomized study of various irradiation doses and fractionating schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. *Cancer* 1980, **45**, 2744–2753.
2. Marcial VA, Pajak TF, Kramer S, *et al*. Radiation Therapy Oncology Group (RTOG) studies in head and neck cancer. *Semin Oncol* 1988, **15**, 39–60.
3. Levitt SH, Frazier AB, James KW. Split-course radiotherapy in the treatment of carcinoma of the esophagus. *Radiology* 1970, **94**, 433–435.
4. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
5. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
6. Cox DR. Regression models and life-tables. *J R Stat Soc* 1972, **B34**, 187–202.
7. Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for esophageal cancer. *Chest* 1995, **107**, 224S–232S.
8. Ajani JA. Contributions of chemotherapy in the treatment of carcinoma of the esophagus: results and commentary. *Semin Oncol* 1994, **21**, 474–482.
9. Kok TC. Chemotherapy in esophageal cancer. *Cancer Treat Rev* 1997, **23**, 65–85.
10. Bleiberg H, Conroy T, Paillot B, *et al*. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer* 1997, **33**, 1216–1220.
11. Douple EB, Richmont RC. Platinum complexes as radiosenzitizers of hypoxic mammalian cells. *Br J Cancer* 1987, **37**, 98–102.
12. Laverick M, Nias AHW. Potentiation of the radiation response of hypoxic mammalian cells by cis-dichlorobis(isopropylamine) trans-hydroxy platinum. *Br J Radiol* 1981, **54**, 529–534.
13. Kolarić K, Nagy B, Roth A, Županc D, Luetić J, Tometič Z. Combined cis-platinum plus radiation antitumor activity in locoregionally advanced squamous cell esophageal cancer. *Oncology* 1988, **45**, 276–280.
14. Cooper JS, Guo MD, Herskovic A, *et al*. Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999, **281**, 1623–1627.
15. George SL. The required size and length of a phase III clinical trial. In Buyse ME, Staquet MJ, Sylvester RJ, eds. *Cancer Clinical Trials Methods and Practice*. Oxford Medical Publications, 1988, 382–406.
16. Roussel A, Bleiberg H, Dalesio O, *et al*. Palliative therapy of inoperable oesophageal carcinoma with radiotherapy and methotrexate: final results of a controlled clinical trial. *Int J Radiat Oncol Biol Phys* 1989, **16**, 67–72.