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Randomised trial of sequential *versus* concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973)

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ABSTRACT

Methods: One hundred and fifty-eight patients were randomised to receive two courses of Gemcitabine (1250 mg/m^2 days 1, 8) and Cisplatin (75 mg/m^2 day 2) prior to, or daily low-dose Cisplatin (6 mg/m^2) concurrent with radiotherapy, consisting of 24 fractions of 2.75 Gy in 32 days, with a total dose of 66 Gy.

Results: Acute haematological toxicity grade 3/4 was more pronounced in the sequential (S) (30% *versus* 6%), oesophagitis grade 3/4 more frequent in the concurrent (C) arm (5% *versus* 14%). Late oesophagitis grade 3 was 4% (S and C), pneumonitis grade 3/4 14% (S) and 18% (C). Because of the poor power of the study no significant differences in median survival (MS), overall survival (OS) and progression-free survival (PFS) could be detected. MS was 16.2 (S) and 16.5 (C) months, 2-year OS was 34% (S) and 39% (C), 3-year OS was 22% (S) and 34% (C).

Conclusion: Radiotherapy 66 Gy given concurrently with daily low-dose Cisplatin or after two courses of Gemcitabine/Cisplatin was well tolerated. Due to early closure no conclusions can be reached on the relative merits; both arms showed good OS.

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1. Introduction

Until the mid 1980s standard treatment of patients with inoperable locally advanced non-small cell lung cancer (NSCLC) consisted of radiotherapy alone. Survival figures doubled when radiotherapy was preceded by platinum-containing chemotherapy.[7,15,17,20] Chemotherapy given concurrently with radiotherapy resulted in a significant improvement over radiotherapy alone also, as was shown in the European Organisation for Research and Treatment of Cancer (EORTC) 08844 study.[21] However, the split-course radiotherapy regimen used in EORTC 08844 study was considered as sub-optimal.

In the following phase II EORTC 08912 study, the feasibility of dose escalation from 55 Gy to 66 Gy was investigated using a concomitant boost technique.[24] This resulted in a radiotherapy fractionation schedule of 66 Gy given in 24 fractions in an overall treatment time (OTT) of 32–34 days, combined with daily Cisplatin (6 mg/m^2), at total dose of 144 mg/m^2.

We started a randomised trial to compare concurrent chemo-radiotherapy (CRT) and sequential CRT for inoperable NSCLC patients stages I–III.

2. Patients and methods

Patients with inoperable NSCLC stage T1-4N0-3 (excluding N3 disease based on supra-clavicular nodes) were randomised to receive sequential or concurrent CRT. All patients had good prognostic features (weight loss $\leqslant$10% in the preceding 3 months and WHO 0 or 1). All patients had a $FEV_1 \geqslant 1$ l and a diffusion-capacity of 60% at least.

The trial protocol was approved by the EORTC Protocol Review Committee and by the medical ethics committees of the participating institutions. Patients were randomised after written informed consent. Randomisation was stratified for performance status (0 *versus* 1), TNM stage (I and II *versus* III) and institution. Patients scheduled for sequential CRT received two courses of Gemcitabine (1250 mg/m^2 days 1,8) and Cisplatin (75 mg/m^2 day 2) with a 3 weeks interval. The concurrent CRT consisted of daily low-dose Cisplatin (6 mg/m^2) 1–2 hours before each fraction. In both treatment arms, the patients received accelerated high-dose conformal radiotherapy; 66 Gy in 24 fractions (2.75 Gy per fraction) in 32 d. Elective nodal irradiation (40 Gy in 20 fractions) was given; for N0 disease, the homo-lateral hilar region, for N1- or N2 disease, the mediastinum (with the exception of the lower para-oesophageal lymph nodes). For N2 disease the homo-lateral supra-clavicular area was included as well. The elective nodal irradiation was given with two opposing anterior–posterior fields. The daily dose to the GTV was 2.75 Gy, resulting in a dose of 55 Gy to the GTV after 20 fractions. Then a boost to the GTV was given of four fractions of 2.75 Gy up to 66 Gy. The length of the oesophagus irradiated in the elective fields was restricted to 18 cm, while the length of the oesophagus in the boost fields was restricted to 12 cm.[24]

2.1. Baseline and response evaluation

Within 4 weeks before the start of treatment and 6 weeks after the end of the irradiation a medical history, physical examination, performance status, laboratory values, chest X-ray, bronchoscopy, CT-scan of the thorax and upper abdomen, lung-function and a quality-of-life questionnaire were obtained.

Acute and late toxicities were scored using the RTOG/EORTC criteria. After completion of the treatment, patients were followed every 2 months until disease progression or death.

2.2. Statistical analysis

Primary endpoint of this trial was overall survival. Secondary endpoints included disease-free survival, local control, acute and late toxicities, and quality of life. Statistical considerations of the protocol were as follows: assuming a 1-year survival in the control group (concurrent CRT and daily Cisplatin) of approximately 45%, 189 deaths per arm (total 378 deaths) were calculated to detect an absolute increase of 10% in the 1-year survival, i.e. from 45% to 55% with two-sided type I error of 0.05 and a power of 80%.

Following the recommendations of the Independent Data Monitoring Committee, the Lung Cancer Group and the EORTC Executive Committee decided to terminate this trial prematurely after inclusion of 158 patients due to poor accrual.

Primary analysis of overall survival was based on the intent-to-treat principle. Overall survival was defined by the time interval between randomisation and death due to any cause calculated according to the Kaplan–Meier method. Patients still alive at the time of the analysis were censored at the last date known to be alive. Progression-free survival was measured from randomisation until progression or death due to any cause (whichever occurred first). Patients alive and without progression at the time of the analysis were censored at the last date known to be alive.

3. Results

3.1. Patients characteristics

Between February 1999 and March 2003, 158 patients were randomly assigned between concurrent and sequential CRT (Fig. 1). Patient characteristics are presented in Table 1. There was imbalance in stage distribution over the two treatment arms. In the sequential arm, 47.4% of the patients had stage-IIIB disease and in the concurrent arm this percentage was 63.8%. In 12.5% of the patients treated with concurrent CRT N3-disease was diagnosed, this percentage was 4% in the patients treated with sequential CRT. The delay between the date of diagnosis (pathology-report) and the randomisation was median 34 d in the sequential CRT arm and 29 d for the patients treated in the concurrent CRT arm. For 16.5% of all patients randomised, this delay was more than 56 d (equally divided over both treatment arms). Data of the treatment compliance are shown in Table 2. Delays between randomisation and start of treatment were median 7 days in the sequential and 19 days in the concurrent arm. A total of 76 patients (97.4%) in the sequential arm and 66 (82.5%) in the concurrent arm actually started protocol treatment.

3.2. Acute and late toxicities

Toxicity was scored for all patients who started protocol treatment (76 patients in the sequential arm and 66 patients in the

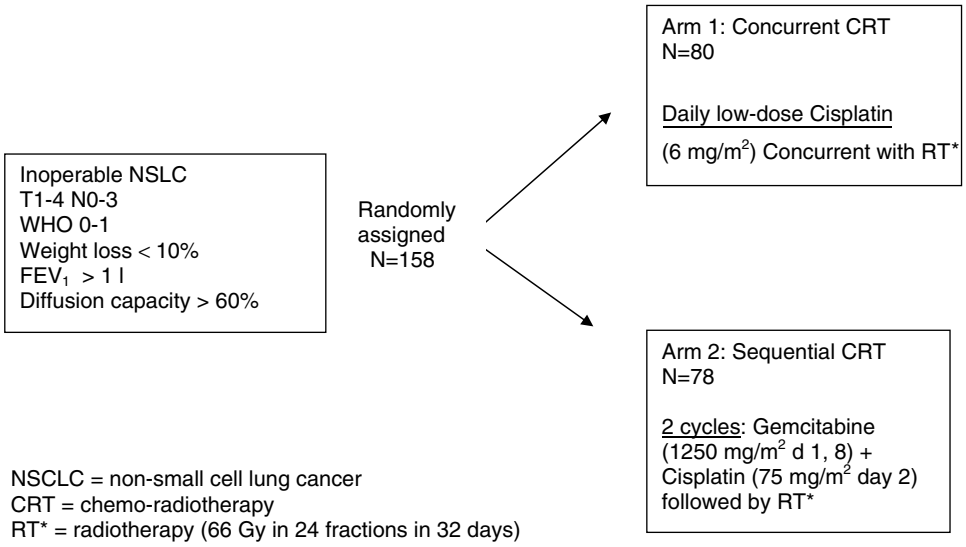


Fig. 1 – EORTC 08972-22973 treatment scheme.

concurrent arm). Severe acute non-haematological toxicity is presented in Table 3A and severe acute haematological toxicity is presented in Table 3B. Acute oesophagitis grade 3 occurred in 9 patients (14%) and grade 4 in 2 patients (3%) in the concurrent arm. In the sequential arm only 4 patients (5%) developed acute oesophagitis grade 3 and no grade 4 oesophagitis was scored.

Table 1 – Characteristics of randomised patients (N = 158)

Characteristic	Sequential arm (N = 78) (%)	Concurrent arm (N = 80) (%)
Age (years)		
Median	64	62
Range	(46–78)	(36–78)
Sex		
Male	78	74
Female	22	26
WHO performance		
0	42	44
1	58	56
Lung function		
FEV_1 (median) (l)	2.3	2.1
Diffusion capacity (median) (%)	81	79
Clinical Stage		
I	3	1
II	4	5
IIIA	45	30
IIIB	47	64
Unknown[a]	1	0
Histology/cytology		
Squamous	40	40
Adenocarcinoma	32	24
NSCLC not specified	19	34
Mixed adeno squamous	1	0
Other	8	3
Delay diagnosis-randomisation		
⩽ 30 d	41	55
⩽ 56 d	42	29
> 56 d	17	16

a This patient had a local recurrence after lobectomy (T2N0 status).

Acute haematological toxicity was more pronounced in the sequential arm with the occurrence of severe granulocytopenia grade 3 in 13 patients (17%) and grade 4 in 3 patients (4%). The median granulocytes values were 1.5 (S) (range 0.4–7.9) and 3.5 (C) (range 0.8–9.6). In 4 patients acute non-haematological toxicity was the main reason for stopping protocol treatment.

Late toxicity data are summarised in Table 3C. The higher incidence of severe acute oesophageal toxicity in the concurrent arm did not result in a higher incidence of severe lat toxicity. Late oesophagitis grade 3 occured in 4% and 5% of the patients in the sequential and concurrent arm, however, grade 1 and grade 2 were more frequent in the concurrent arm (22% *versus* 11%). Other late toxicities consisted of pain in the chest and/or shoulders and were slightly more frequent in the concurrent arm (15% *versus* 8%). Two patients in the sequential arm developed late grade 4 cardiac toxicity. Fatal lung-haemorrhage, possibly treatment related, was observed in one patient treated in the sequential and in one patient treated in the concurrent arm.

3.3. *Clinical response, overall survival and progression-free survival*

A complete or partial response (according to the WHO-criteria) was achieved in 53 patients in the sequential treatment arm and 40 patients in the concurrent arm. Considering all patients who started protocol treatment, this corresponds to a response rate of 69.7% (95% confidence interval (CI): 58.1–79.8) for the sequential treatment and 60.8% (95% CI: 47.8–72.4) for the concurrent treatment ($p = 0.29$).

At 39 months of median follow-up, the incidence of loco-regional tumour progression (S: 43%; C: 46%) and the development of distant metastases (50% in both arms) were similar for both treatment groups.

Table 2 – Protocol adherence, treatment delay and overall treatment time radiotherapy

	Sequential arm number of patients (%)	Concurrent arm number of patients (%)
All patients	78	80
Treatment not started	0	12
No chemotherapy	0	2
No radiotherapy	2	0
Chemo/radio started	76 (97%)	66 (83%)
Full dose chemotherapy	64 (84%)	54 (82%)
Full dose radiotherapy	74 (97%)	64 (97%)
	Sequential arm ($N = 76$) median number of days (range)	Concurrent arm ($N = 66$) median number of days (range)
Delay randomisation-start CT	7 (1–20)	19 (4–47)
Delay randomisation-start RT	62 (44–97)	19 (4–47)
Overall treatment time RT	32 (12–42)	32 (22–38)

Table 3A

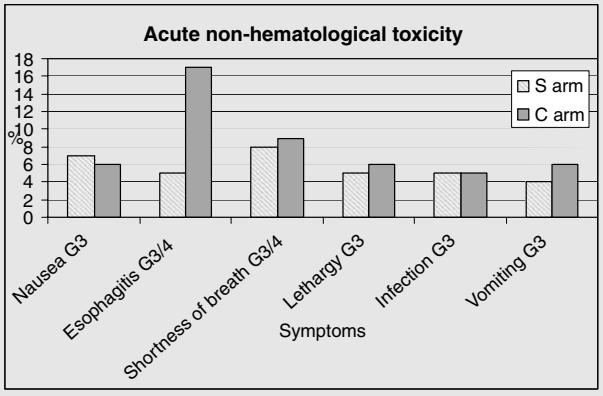
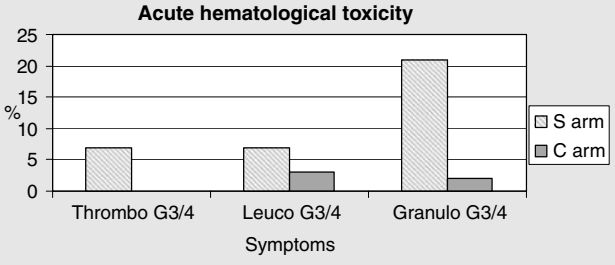
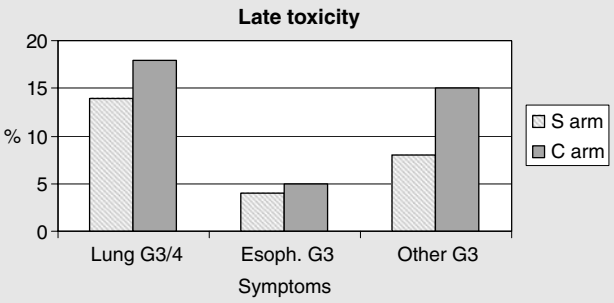


Table 3B



At the time of this analysis, 62 patients (79.5%) in the sequential arm and 58 patients (72.5%) in the concurrent arm have died. The median survival for the sequential and concurrent arm was 16.2 months (95% CI: 12.8–22.6) and 16.5 months (95% CI: 11.3–24.3), respectively. The 1-year survival for the sequential and concurrent arm was 69% (95% CI: 58.7–79.3) and 55.9% (95% CI: 45.0–66.9), respectively, the 2-year survival 33.6% (95% CI: 23.0–44.2) and 38.5% (95% CI: 27.6–49.4), respectively, and the 3-year survival was 21.6% (95% CI: 12.0–31.2) and 29.2% (95% CI: 0–43.1), respectively

Table 3C



(Fig. 2A). We observed a hazard ratio of 1.06 (95% CI: 074–1.52) (see Fig. 3).

With 65 events in the sequential arm and 70 in the concurrent arm, a median progression-free survival of 10.8 months (S) (95% CI: 9.0–15.0) and 8.5 months (C) (95% CI: 6.4–10.9) was observed and a 1-year PFS of 44.5% (S) (95% CI: 33.4–55.6) and 36.3% (C) (95% CI: 25.7–46.8), corresponding to a hazard ratio of 0.79 (95% CI: 0.56–1.10).

4. Discussion

The question whether CRT should be given in a sequential or concurrent way has not been answered in this trial. Unfortunately, our study with a total of 158 patients randomised and 120 deaths reported was underpowered and results need to be interpreted carefully.

Severe acute haematological toxicity was more pronounced in the sequential treatment and consisted mainly of severe granulocytopenia. This did not lead to an increase of clinical symptoms. In the meta-analysis of Rowell no significant difference in neutrocytopenia was observed between sequential and concurrent CRT.[19] However, in this analysis standard poly-chemotherapy schedules were compared, with higher doses of chemotherapy in the concurrent treatment arms than those used in our study.

Severe acute oesophagitis in our study was more frequent in the concurrent treatment arm. Late oesophageal toxicity

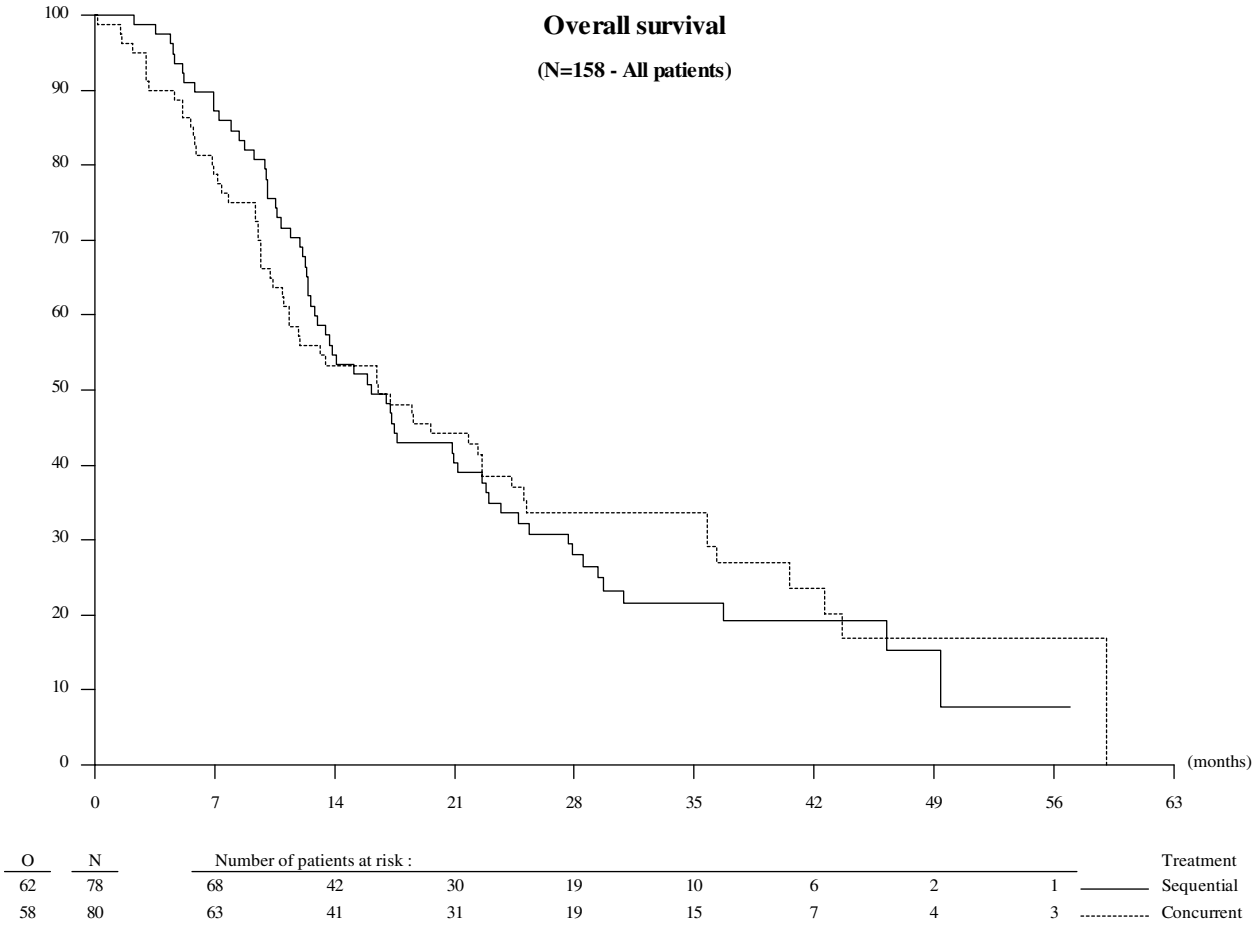


Fig. 2 – Overall survival by treatment group.

grade 1 or grade 2 was more frequent in the concurrent arm but with similar occurrence of late grade 3 toxicity. This is in agreement with data from the meta-analysis of concurrent *versus* sequential CRT.[19]

Severe late pulmonary toxicity was similar in both treatment arms. This is in agreement with the results of the meta-analysis of Rowell.[19] In this analysis the incidence of lung fibrosis and/or radiation pneumonitis was not significantly different for sequential or concurrent CRT.

Several phase-III studies examined the optimal way of combining chemotherapy with radiation. Published randomised trials comparing concurrent *versus* sequential chemoradiotherapy are summarised in Table 4.

In 2005, the locally advanced multi-modality protocol (LAMMP) trial demonstrated the superiority of concurrent CRT if Paclitaxel and Carboplatin were used.[3]

The survival results of sequential CRT in this study compare favourably to the data of Fournel and Zatloukal. In this trial, Cisplatin and Gemcitabine were given, while in the other studies a combination with a Vinca-alkaloid was used.[6,9,10,26] The combination of Gemcitabine and Cisplatin has reported response rates up to 80%. A meta-analysis of different chemotherapy combinations suggested that the combination of Cisplatin with Gemcitabine might be more active than other platinum combinations.[5,16,25]

In this trial, however, we did not use standard chemotherapy but low-dose Cisplatin as a radio-sensitiser in the concurrent arm. In the meta-analysis of Rowell, a combination of concurrent low-dose Cisplatin (<150 mg/m^2) or Carboplatin (<700 mg/m^2) with irradiation appeared to be ineffective to improve outcome compared to radiotherapy alone. Indeed several low-dose platinum-based trials were negative, but in these schedules Carboplatin was used.[1,4,8] Even using a high-dose of Carboplatin 840 mg/m^2 with continuous infusion, Groen et al. could not demonstrate improved survival.[12] Another trial with Cisplatin (daily 6 mg/m^2) was negative also, but the administered radiation dose was 45 Gy only.[23] This might indicate that Cisplatin is a more potent radio-sensitiser than Carboplatin. This is supported by the results of concurrent CRT in cervix cancer where a combination with Cisplatin is used as well.[11] The addition of 5-FU to Cisplatin did not result in better survival, but was more toxic.[11] In head and neck cancer the benefit of adding chemotherapy to radiation therapy on patient survival compared with radiotherapy alone has been demonstrated by a large meta-analysis of trials.[18] Interestingly, the survival benefit was confined to the concurrent use of chemotherapy and radiotherapy. In summary, a combined use of chemotherapy and radiotherapy in the treatment of solid tumours favours concurrent CRT.[2]

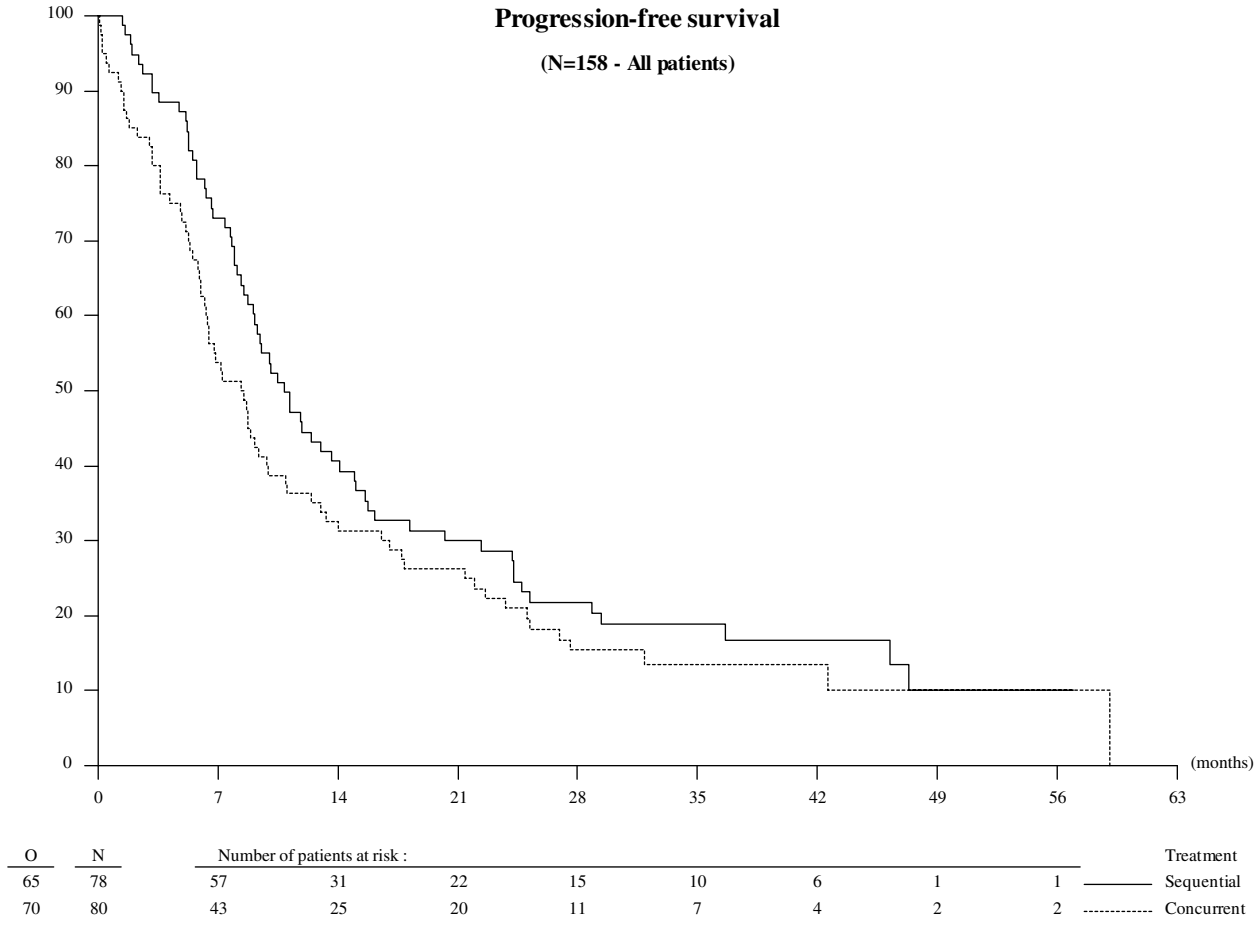


Fig. 3 – Progression-free survival.

Table 4 – Published randomised trials comparing concurrent (C) chemo-radiotherapy versus sequential (S) chemo-radiotherapy, the number of patients included (N) and the 1- and 2-year survival rates

Author	N	1-year survival (%)		2-year survival (%)	
		C	S	C	S
Furuse et al. [10]	320	65	56	37	29
Curran et al. [6]	402	63	57	37	31
Zatloukal et al. [26]	102	69	53	34	14
Fournel et al. [9]	205	56	56	35	23
EORTC 08972-22973	158	56	69	39	34

In the Cochrane meta-analysis, the chemotherapy intensity (daily, weekly, two- or four-weekly) had no influence on the relative risk of survival, although a trend was seen for a better outcome if the chemotherapy was given more frequently.[19]

In our study, the radiotherapy dose applied was high (66 Gy), and the OTT of 32–34 d was short compared to the other studies. The Biological Equivalent Dose of 66 Gy in fractions of 2.75 Gy equals 70 Gy in fractions of 2 Gy for an α/β ratio of 10 Gy. Furuse used a dose of 56 Gy in fractions of 2 Gy and a split course. Curran and Zatloukal prescribed 60 Gy in 2 Gy per fraction. Fournel applied a dose of 66 Gy in fractions of 2 Gy, with an OTT of 45 d. The studies of Schild, Keene and Jeremic, in which high radiation doses were given in short OTT combined with low-dose Cisplatin (5–7.5 mg/m^2) or low-dose Carboplatin and Paclitaxel, showed promising 5-year survival rates of 25%, 23% and 36%, respectively.[13,14,22]

The combination of concurrent low-dose Cisplatin with radiation appears to be a good option, especially if standard poly-chemotherapy together with radiotherapy is not possible, for instance in elderly, frail patients with marginal renal or cardiac function. In our opinion there is no evidence to prove that concurrent standard poly-chemotherapy is superior to daily low-dose Cisplatin alone, if combined with high dose irradiation.

5. In summary

Accelerated high-dose radiotherapy given concurrently with daily low-dose Cisplatin or after two courses of Gemcitabine and Cisplatin was well tolerated in a large group of inoperable NSCLC patients. Delays in starting treatment were longer in the concurrent arm. Because of the premature closure of this trial, no definite conclusions concerning the superiority of concurrent or sequential CRT can be made. Both schedules are active combinations with results similar to other phase III trials comparing sequential *versus* concurrent CRT. A meta-analysis is to be awaited.

Conflict of interest statement

None declared.

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