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Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial☆

H. Bartelink[a,*], W. Van den Bogaert[b], J.-C. Horiot[c], J. Jager[d], M. van Glabbeke[e]

[a]*The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands*
[b]*UZ Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium*
[c]*Centre G.F. Leclerc, 1 Rue du Professeur Marion, 21034 Dijon-Cedex, France*
[d]*Radiotherapeutisch Instituut Limburg, Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands*
[e]*EORTC Data Centre, Ave. E. Mounier 83, 1200 Brussels, Belgium*

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Abstract

A randomised phase II trial was initiated to explore the feasibility of concomitant cisplatin and radiotherapy with conventional fractionation (CF) or multiple fractions per day (MFD) for patients with locally advanced head and neck malignancies. The MFD schedule was designed to achieve higher tumour concentrations of cisplatin at the time of irradiation by reducing the number of radiation treatment weeks from 7 to 3, allowing recovery from side-effects of both irradiation and cystostatic drugs during the rest periods, while keeping the same total dose and overall treatment time. Patients were randomised between a conventional fractionation scheme (CF) of 70 Gy in 7 weeks with 2 Gy per fraction with a daily dose of 6 mg/m^2 cisplatin and a modified fractionation scheme (MFD) delivering three fractions of 1.6 Gy per day, in weeks 1, 4 and 7, keeping the same overall treatment time and total dose. In the modified treatment regime, a daily dose of 10 mg/m^2 cisplatin was administered. 53 patients were entered in this trial and radiotherapy was given according to the schedule to all patients in both treatment arms. Cisplatin was given during the whole course of radiotherapy to only one quarter of the patients in the CF arm, stopping mostly after 5–6 weeks due to bone marrow depression and kidney toxicity, while patients in the MFD arm received it according to schedule. No difference was observed in acute and late toxicity in both treatment arms, while a similar or even better tumour response was obtained with MFD. A 67% higher daily dose of cisplatin concomitant with irradiation could be given in a 3-week multiple fractionation per day schedule, as opposed to the cisplatin given in the conventional daily fractionation schedule of 7 weeks with the same total radiation dose. Similar acute and late toxicities were seen in both treatment arms.

Keywords: Concomitant cisplatin; Radiotherapy; Alternative fractionation

1. Introduction

Improvement of the loco-regional control rate has been sought for patients with advanced head and neck cancer in several trials of the European Organization for Research and Treatment of Cancer (EORTC). Various fractionation schemes were introduced to reach this goal; for example the delivery of multiple fractions per day over a short period to reduce the overall treatment time [1]. An improved local control rate was achieved, as was seen in trials from other groups [2,3].

Another approach was hyperfractionation to spare the normal tissue by reducing the dose per fraction [4]; in this way, a higher tumour dose could be delivered to patients with oropharynx tumours, leading to a significantly higher loco-regional control rate and a better survival rate. These approaches were recently confirmed by a four arm randomised trial study of the Radiation Therapy Oncology Group (RTOG) [2]. Further improvement has also been sought by combining radiotherapy and cytostatic drugs.

☆ This study was conducted on behalf of the Cooperative Group for Radiotherapy of the EORTC (European Organization for Research and Treatment of Cancer).

* Corresponding author. Tel.: +31-20-512-2122; fax: +31-20-669-1101.

E-mail address: h.bartelink@nki.nl (H. Bartelink).

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Experimental studies suggested that cisplatin in combination with radiation could be a powerful drug to enhance tumour cell kill [5]. Possible mechanisms explaining this enhancement included inhibition of DNA repair, hypoxic cell sensitisation, or simply independent cell killing. The largest tumour effects in animals have been observed when cisplatin was given daily, just before each irradiation [6]. Enhancement appeared to be strongly drug-dose dependent, i.e. the higher the cisplatin dose, the larger the enhancement. A limitation was that acute and sometimes-late normal tissue damage was increased when cisplatin and irradiation were used simultaneously [7,8]. Normal tissue damage was, however, increased to a lesser extent than the increased tumour cell kill [6]. Encouraged by the above results, clinical trials were undertaken in various tumour sites. In 1992, we demonstrated an improvement in local control and survival by the daily use of concomitant cisplatin and radiotherapy in patients with lung cancer [9]. During the last few years, the efficacy of concomitant radiotherapy and cisplatin was confirmed in several lung, head and neck and cervical cancer trials [10–15]. The present study is a report of a randomised phase II trial for locally advanced head and neck cancer to further optimise this combined modality treatment. In this trial, two different fractionation schemes have been used; one arm with conventional fractionated irradiation (CF) during seven weeks, and the other arm with three fractions per day (MFD) given in weeks 1, 4 and 7 with rest periods of 2 weeks in between. In both arms, cisplatin was given one hour before the irradiation. The fractionation schedule with three fractions per day was previously tested, together with other fractionations schedules, which were designed to decrease the overall side-effects without losing loco-regional control [16].

The purpose of this trial was two-fold:

1. To assess the feasibility of a new fractionation schedule that reduced the number of treatment weeks from 7 to 3, to permit the delivery of higher doses of cisplatin during the irradiation period, allowing recovery from the side-effects of both irradiation and cytostatic drugs during the rest periods, while keeping the same total dose and overall treatment time.
2. To compare the acute and late toxicity between the modified and conventional fractionation schedules both given concomitantly with a daily dose of cisplatin.

2. Patients and methods

Patients were randomised between:

I. Conventional fractionated irradiation with 2 Gy per fraction, preceded daily by 6 mg/m^2 cisplatin, or

II. Three fractions per day of 1.6 Gy per fraction and 10 mg/m^2 cisplatin, given daily between the first and the second session. In this arm, the overall treatment time was also seven weeks, but treatment was only given in weeks 1, 4 and 7. The time interval between each fraction varied between 3 and 4 h.

In Arm I, the total dose was 70 Gy and in Arm II 72 Gy (Fig. 1). Patients in Arm I (CF) were given daily cisplatin intravenously (i.v.) on an outpatient basis; no special hyperhydration was prescribed although a minimum intake of 2 l of fluid was required. Patients receiving MFD in Arm II were hospitalised and were given daily 3–4 l fluid i.v. 53 patients were randomised[1] (Fig. 2). 4 patients were ineligible for the trial (2 patients with a poor performance status, 2 patients with an inappropriate stage or histology) and were therefore excluded from further analysis. This study included patients with locally advanced, inoperable head and neck cancer of the oral cavity, oropharynx, larynx and hypopharynx (Table 1).

One institute[2] that could not participate in the MFD arm of the trial was allowed to register 8 patients in the CF arm. These data will be reported separately in Tables 2 and 3 as 'CF non-randomised'.

The EORTC/RTOG scale was used for scoring the acute and late side-effects. The side-effects and local

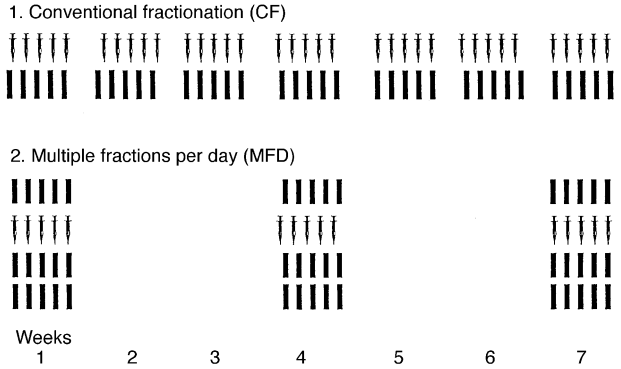

Fig. 1. Treatment schedule: CF:XRT 70 Gy in 7 weeks (▌= daily radiation dose: 2 Gy). ▌ CDDP 6 mg/m^2 intravenously (i.v.) 30–60 min before each irradiation. MFD:XRT 72 Gy; dose per fraction: ▌= 1.6 Gy; dose per week: 24 Gy on weeks 1, 4 and 7. ▌ CDDP 10 mg/m^2 i.v. per day, between the first and second irradiation. XRT, radiotherapy.

[1] Participating Centres: Netherlands Cancer Institute, Amsterdam; Algemeen Ziekenhuis Middelheim, Antwerp; Centre G.F. Leclerc, Dijon; Radiotherapeutisch Instituut Limburg, Heerlen; Centre Hopitalier de Tivoli, La Louvière; Free University Hospital, Amsterdam, Hopital La Timone, Marseilles; Bernard Verbeeten Institute, Tilburg; Centre Hospitalier, Lorient; Centre Leon Bdrard, Lyon; Academisch Medisch Centrum, Amsterdam.

[2] Institute Gustave Roussy, Paris.

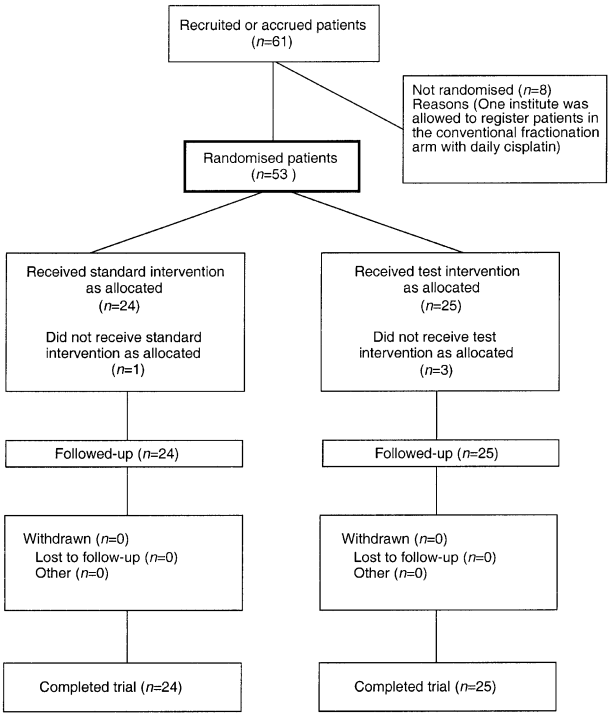

Fig. 2. Flow chart of the progress of patients through the trial.

control were estimated as a fraction of time by the Kaplan–Meier method. Patients who never reached a complete tumour response were considered treatment failures at the end of therapy.

The principle end-point was the occurrence of acute and late side-effects. 30 patients had to be randomised in each arm to be able to observe at least once (with a 95% Confidence Level) any acute or late side-effect that would generally occur in 10% or more of a general population submitted to the same therapy.

3. Results

3.1. Overall results

Radiotherapy was considered 'stopped' when less than 95% of the total intended dose was administered. This occurred in 2 patients in the CF arm and in 7 patients in the MFD arm. Treatment was considered 'prolonged' if the total treatment duration was prolonged by at least 1 week (7 days). This happened in 8 patients in the CF arm and in 2 patients in the MFD arm. In the MFD arm, radiotherapy is reported as 'delayed' if the delay was >3 days. This occurred in the MFD schedule in 2 patients, but the total treatment duration was not prolonged. In 14 patients in each of the treatment arms, radiotherapy could be given according to schedule.

Table 1
Patient characteristics

Treatment arm		CF	MFD
Patients (*n*)		24	25
Sex			
Male		17	21
Female		7	4
PS (Performance status)			
0		14	11
1		9	7
2		1	7
Histology			
Well differentiated		12	8
Moderately differentiated		8	5
Poorly differentiated		4	9
Inevaluable		0	3
Tumour location			
Oral cavity		11	5
Oropharynx		9	14
Larynx		3	1
Hypopharynx		1	4
Other		0	1
T classification			
T2		1	0
T3		9	5
T4		14	20
N classification			
No		4	7
N1		7	7
N2		6	5
N3		7	6
Largest diameter (mm) of:			
Tumour	Median (range)	50 (30–98)	58 (40–90)
Lymph nodes	Median (range)	25 (10–90)	54 (20–80)
Disease	Median (range)	50 (25–98)	60 (20–90)

CF, Conventional fractionation; MFD, Multiple fractions per day.

In the CF-randomised group, 1 patient refused protocol treatment and radiotherapy was stopped at 47 Gy for general toxicity. Treatment was delayed because of local toxicity in 3 patients and for both local and renal toxicity in 1 case. In 1 patient, treatment was delayed 3 times because of tracheostomy, fever and technical reasons (resulting together in 1 week treatment prolongation). In the 3 other cases, delays were not related to treatment. In the MFD group, 1 patient refused protocol treatment, 2 patients discontinued therapy after the first series (because of progression or acute respiratory distress syndrome) and 1 patient discontinued therapy after the second series for local toxicity. The third series was incomplete in 3 patients (patient compliance, holiday, reason not reported). In 1 patient, the surgeon attempted to remove a lymph node and the third series was delayed for postoperative complications. In I patient, the last series was delayed, but this was probably unrelated to treatment (Table 2).

Table 2
Treatment modifications per treatment arm; delivered cisplatin dose as a % of the prescribed protocol dose, and number of patients completing radiotherapy treatment

DDP/STOP	CF-randomised	MFD-randomised	CF-non randomised[a]
No XRT/no DDP	1	1	
00–80%	7 (6 full dose XRT, 1 stopped)	6 (5 full dose XRT, 1 stopped)	2
81–95%	10 (full dose XRT)	1 (full dose XRT)	3
>95%	6 (6 full dose XRT)	17 (12 full dose XRT, 5 stopped)	3
Total	24	25	8

CF, conventional fractionation; MFD, Multiple fractions per day; XRT, radiotherapy; DDP, cisplatin.
[a] CF non-randomised 8 registered patients from one institute that did not participate in the randomisation.

3.2. Treatment

Reasons for stopping cisplatin, mostly in the last 2 weeks of irradiation, were bone marrow depression in 6 patients, deterioration of kidney function in 6 patients, and gastro-intestinal toxicity in 2 patients, general toxicity in 1 patient and protocol violation in 1.

3.3. Acute toxicity

The general side-effects of cisplatin were bone marrow depression and kidney toxicity necessitating modification of the treatment prescription as described above; however, recovery was seen in all patients. Grade III-IV leucopenia was observed in 9 patients in the CF arm (randomised) and in none of the patients in the MFD arm. Grade III-IV thrombocytopenia has been seen in 1 patient in each treatment arm.

Acute mucositis developed earlier in patients treated with three fractions per day; however, the reaction was less intense; which was scored by physicians as objective mucosal reaction. Diffuse mucositis was observed in 8 patients in the CF arm (randomised) and in 6 patients in the MFD arm. The worst score for functional mucosal reaction (oral alimentation impossible) was observed in 7 patients in the CF arm and in 3 patients in the MFD arm. The clinical observations of mucositis correspond with the complaints of the patients, recorded as functional mucosal reaction on a four-point scale. The changes of weight and performance status were similar in both arms.

3.4. Late side-effects

Two patients treated with MFD died due to severe complications, 1 from larynx necrosis, and 1 from sepsis after mandibular necrosis. The first patient had an extensive laryngeal tumour with cartilage invasion; the second patient had an extensive oral cavity tumour with invasion of the bone before the start of radiotherapy (Table 3).

More grade 4 complications were seen in the MFD Arm; however, an actuarial plot of all grade 3 and 4 complications showed a similar profile in both treatment arms (Fig. 3).

3.5. Loco-regional control and survival

All loco-regional relapses were observed during the first 2 years after the end of treatment. Locoregional control rates were slightly better in patients treated with three fractions per day (Fig. 4). No significant difference was observed in survival between the two randomised treatment groups (Fig. 5).

3.6. Causes of death

Most of the patients died from their malignant disease. 2 patients died in the MFD group of late complications (necrosis), 1 year after registration. One patient died of infection 7 months after the start of treatment; in this last case, progression was suspected but not confirmed.

4. Discussion

The results of this trial demonstrate the feasibility of giving a 67% higher cisplatin dose at the time of irradiation using a multiple fractions per day irradiation schedule in patients with head/neck cancer compared with giving cisplatin during a conventional daily fractionation schedule.

A similar tumour response and acceptable acute and late toxicity have been obtained in patients treated in only 3 weeks. This new treatment regimen, using the same total dose as the conventional fractionation schedule of 70 Gy, and the same overall treatment time of 7 weeks may be used for testing new radiosensitisers, or combinations with chemotherapy. The advantage of this condensed irradiation regimen is that it allows for recovery of acute side-effects during the rest period, while higher drug doses can be given during the irradiation course, keeping the total dose and overall treatment time the same. This treatment schedule with three

Table 3
Severe complications per treatment arm

Severe complications	CF-randomised	MFD-randomised	CF-non randomised[a]
Mucosal necrosis	1	2	2
Skin and connective tissue ulceration	1	1	0
Muscular fibrosis	2	4	2
Lymphatic drainage problems—severe oedema	3	3	0
Larynx complications—severe oedema requiring tracheostomy	1		2
Dysphagia—requiring dilation. obstructive requiring permanent tube feeding	1	2	3
Pain, severe or intractable	2	6	3
Bone complications—formation of sequestrum or fracture	1	4	0
Neurotoxicity—severe paresthesia/mild weakness		1	0

[a] CF non-randomised, 8 registered patients from one institute that did not participate in the randomisation.

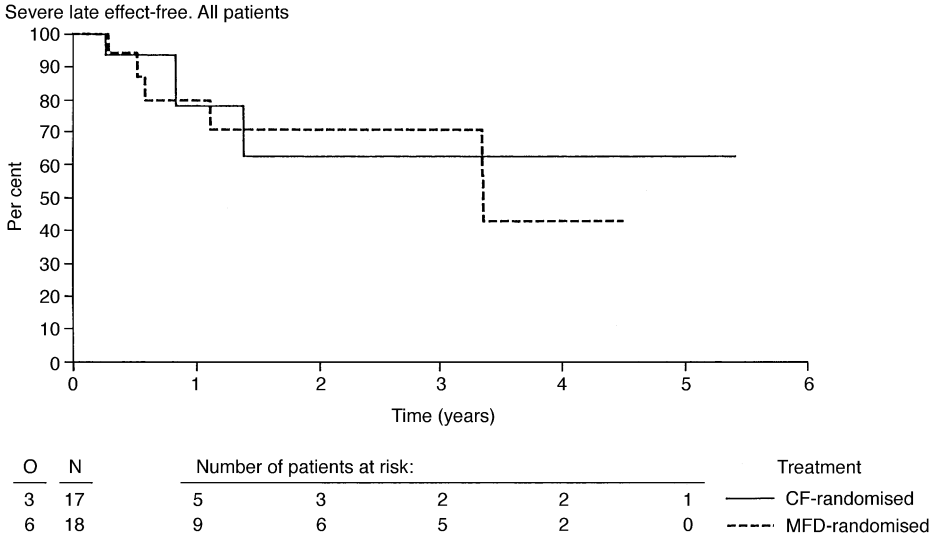

Fig. 3. Severe late effect-free survival per treatment arm. O, observed; N, number; CF, conventional fractionation; MFD, multiple fractions per day. (Only patients who are tumour free for 3 months or more are analyzed.)

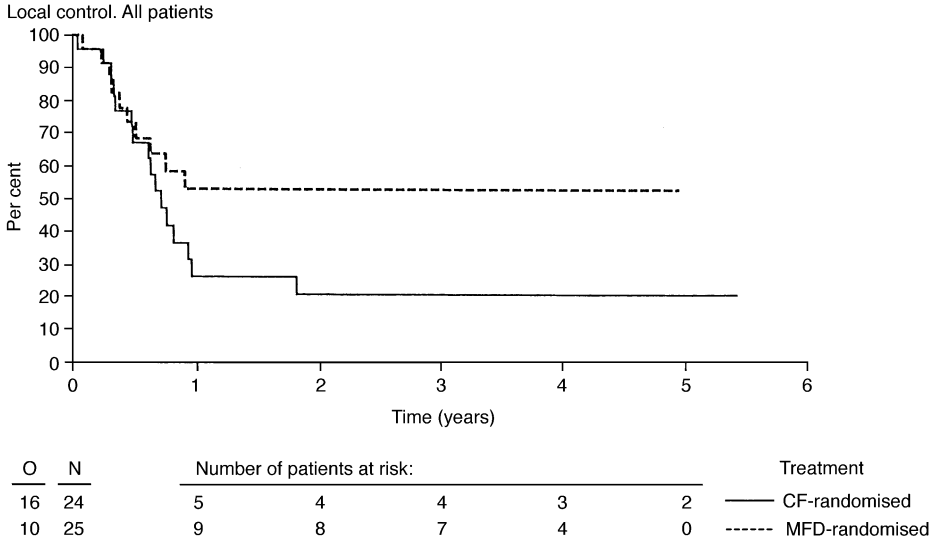

Fig. 4. Local control per treatment arm. O, observed; N, number; CF, conventional fractionation; MFD, multiple fractions per day.

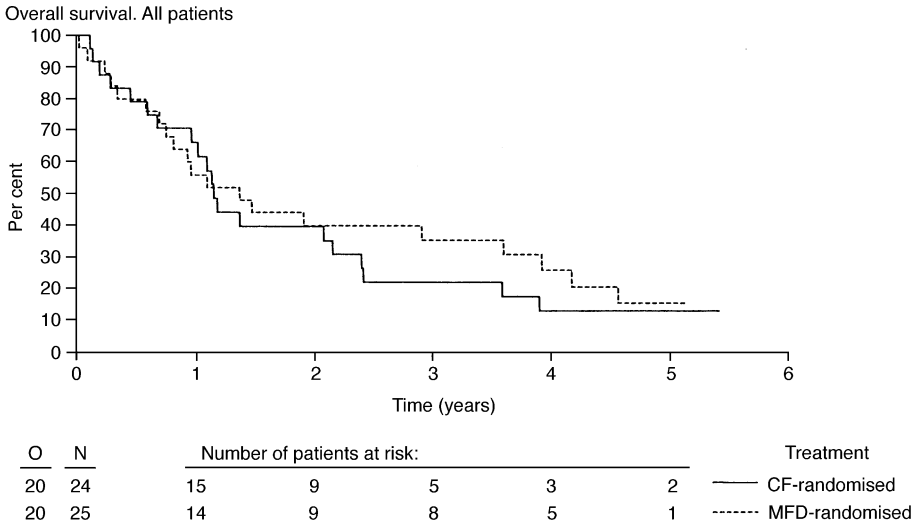

Fig. 5. Overall survival per treatment arm. Overall survival estimate is summarised in the following graph for the three groups of patients.

fractions per day appeared to be feasible as a routine treatment in all participating institutes.

Side-effects of cisplatin such as bone marrow depression and kidney damage were only temporary, while no extremely severe acute radiation reactions were observed. Late normal tissue complications were similar in both treatment arms and were therefore not dependent on the fractionation schedule used. They were probably more related to tumour extension and bone and cartilage invasion. However, it should be noted that the time interval between irradiation fractions was 3–4 h. Animal studies have demonstrated that the half time for slow repair of radiation damage is longer than 3–4 h; therefore an interval of 6 h between fractions would be more appropriate. More late complications may therefore be expected with a shorter time interval. These experimental data are in-line with our previous findings in a trial comparing conventional fractionation with accelerated fractionation, with 3 hours between fractions.[1] The results demonstrated an improved local control and survival, but at the price of more acute and late toxicities.

The apparent (but not significant) superiority of the better local control in the three fractions per day regimen may be the result of selection since more patients with well-differentiated oral cavity tumours were included in the conventional fractionation arm. It should be underlined that this trial was not designed to formally compare therapeutic groups.

Different schedules giving chemotherapy before or after radiotherapy have been extensively investigated in phase III trials for head and neck cancer patients. Despite promising results in phase II trials, no improvement in local control and survival has been achieved in the majority of the trials [14].

In contrast, there is increasing evidence that the concomitant use of chemotherapy, and radiotherapy, as explored in this trial, may improve both loco-regional control and survival. This was seen in 1992 in our EORTC lung trial, when cisplatin, given daily concomitantly with irradiation, improved local control and survival. Several studies in head and neck [10–15], anal and cervical cancer have confirmed these findings. Nevertheless, for advanced tumours, such as those entered in this trial further improvements in the local control rate are needed.

One of the main reasons for the still limited effects of the combination of cisplatin and irradiation may be the relatively low concentration of cisplatin in human tumours when given i.v., compared with that seen in animal experiments [8]. New approaches resulting in higher tumour concentrations of this drug should therefore be explored. One possibility is to give intra-arterial cisplatin weekly concomitantly with irradiation, with *5* doses of 150 mg/m^2 [17,18]. Another approach to increase the efficacy of this combined treatment is the addition of drugs that may further improve the efficiency of the combination, such as tirapazamine [19], or topoisomerase1 inhibitors [20]. A third possibility is to introduce a method of selection in the clinic to determine which patients are sensitive to cisplatin. In all likelihood, a positive effect of the combined use of cisplatin and radiotherapy will only occur in patients with tumours that are sensitive to cisplatin [7]. One can conclude that the measurement of drug concentration and sensitivity to cisplatin should be performed, so the full course of cisplatin and radiation can be given to patients with cisplatin-sensitive tumours. Measurement of cisplatin sensitivity and drug concentration in human tumours has become possible through the development of antibodies against cisplatin DNA adducts [21]. In a group of lung cancer patients, we showed that those with a high concentration of cisplatin DNA adducts in the buccal mucosa had a significantly better prognosis

than those with low concentrations [22]. To optimise the benefit of concomitant radiotherapy, the combination should preferably be used only in patients shown to have a high tumour drug uptake or when the tumour is sensitive to cisplatin.

To conclude, a 67% higher daily dose of cisplatin concomitant with irradiation could be given in a 3-week multiple fractions per day schedule as opposed to a lower daily cisplatin dose given in a conventional daily fractionation schedule of 7 weeks with the same total radiation dose. Similar acute and late toxicities were seen in both treatment arms.

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