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Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy

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Summary

EORTC protocol 22791 compared once daily fractionation (CF) of 70 Gy in 35–40 fractions in 7–8 weeks, to pure hyperfractionation (HF) of 80.5 Gy in 70 fractions in 7 weeks using 2 fractions of 1.15 Gy per day, in T_2–T_3 oropharyngeal carcinoma (excluding base of tongue), N_0, N_1 of less than 3 cm. From 1980 to 1987, 356 patients were entered. In the final analysis (June 1990), the local control was significantly higher ($p = 0.02$ log-rank) after HF compared with CF. At 5 years, 59% of patients are local disease-free in the HF arm compared to 40% in the CF arm. The superiority of HF was demonstrated in patients staged T_3N_0, T_3N_1 but not in T_2. The Cox model confirmed that the treatment regimen was an independent significant prognostic factor for locoregional control ($p = 0.007$ log-rank). This improvement of locoregional control was responsible for a trend to an improved survival ($p = 0.08$ log-rank). There was no difference in late normal tissue damage between the two treatment modalities.

Definition and rationale

If CF is defined as a single fraction of 2 Gy per day, 5 days per week, HF consists of increasing the number of fractions, hence using at least 2 fractions per day with a lower dose per fraction, the overall treatment duration (in days) of the two regimes (CF and HF) being identical. This contrasts with accelerated radiotherapy in which the overall treatment time is reduced, but which also commonly uses a larger number of fractions and a smaller fraction size than for CF.

The rationale for pure hyperfractionation is based on exploiting differences in the radiobiology of tumors and late responding normal tissues. Enhancing the therapeutic differential between the tumor, which responds quickly, and slowly-responding normal tissues depends upon three phenomena: differences in repair capacity, differences in the effect of division cycle redistribution, and an increase in the relative "biological" dose rate to the tumor.

The initial rationale for testing hyperfractionation was based on exploiting the "self-sensitizing" effect of redistribution on the response of proliferative tissues [22]. A dose fraction of 2 Gy selectively sterilizes the subpopulations of cells in more sensitive phases of the division cycle, with the result that the surviving cells are, on average, more radioresistant than the initial population. These surviving tumor cells progress through the division cycle between dose fractions, causing them to redistribute into phases of the cycle which

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are, on average, more radiosensitive than if no such redistribution occurred. Since late responding tissues are not actively proliferative, they would not undergo the same self-sensitization as the tumor. The therapeutic gain that results from using a series of 2-Gy fractions should be enhanced by using even more and smaller dose fractions.

A more powerful rationale emerged when it was appreciated that the non-proliferating target cells of late responding normal tissues show a greater repair of non-lethal injury between dose fractions than do actively proliferating cell populations [1,21,23]. This became apparent from clinical experience and laboratory studies in the 1970s and early 1980s. Severe sequelae developed in late responding tissues if fractionation was limited to a small number of large dose fractions. Conversely, when the total dose was divided into a large number of small fractions, it was possible to increase the tolerance of late responding tissues more than would be predicted from the fractionation response of acutely-responding tissues. These differentials can be quantified using the linear-quadratic cell survival model. Assuming mid-range, α/β values of 4.5 Gy for late responding normal tissues, and 15 Gy for the tumor, a dose of 80.50 Gy in 1.15-Gy fractions would produce late effects equivalent to those from 70 Gy in 2-Gy fractions, whereas a constant tumor control rate would require an increase to only about 73.70 Gy. Thus, the therapeutic gain, expressed in terms of the relative increase in biologic dose to the tumor, would be 80.50/73.70, i.e. about 1.09 or 9%.

Finally, since the overall time is the same in the HF and CF arms, but the biologically-effective tumor dose is increased, the biologic dose rate to the tumor is accelerated by the same 10% as the total biologic dose, equivalent to shortening a 7-week treatment regimen by about 5 days [24].

The feasibility trial

The parameters of the HF regime used in EORTC trial 22791 were established by Horiot et al. [11] in a pilot study of 103 head and neck cancer patients treated from 1975 to 1979 with 2 fractions of 1.15 to 1.25 Gy per day, escalating the total dose from 70 to 80.5 Gy. The lowest dose per fraction (1.15 Gy) allowed the total dose of 80.5 Gy to be given with more tolerable acute mucosal reactions, in a group of patients in whom large target volumes received doses up to 50 Gy. Of interest, this pilot study yielded an improvement in 5-year locoregional control ($p = 0.05$) in the group of patients receiving 80.5 Gy as compared to patients receiving less than 80 Gy. Unfortunately, except for the feasibility of the scheme, no firm conclusion could be drawn because of the lack of stratification per stage and tumor location at each dose level.

Between 1983 and 1987, the RTOG conducted a rather similar trial [6,7] in inoperable head and neck carcinoma, using 2 fractions of 1.2 Gy each per day, escalating doses of 67.2, 72, 76.8 and 81.6 Gy. A 25% 2-year locoregional control was obtained with the 67.2 Gy dose level as compared to 43–45% figures for the 3 higher doses. In this trial, adequate stratification was made by site, nodal and performance status.

Parameters of the phase III trial (EORTC 22791)

Scheme of the trial (Table I)

In arm 1, the treatment regimen (conventional fractionation = CF) consisted of 70 Gy in 35 fractions in 7 weeks. In some cases with large amounts of mucosa in the target volume, the fraction dose could be reduced to 1.8 Gy per fraction, thus increasing the overall treatment time to about 8 weeks. In arm 2, the overall treatment time was the same, 2 fractions of 1.15 Gy being delivered per day with a 4–6 h gap between the 2 fractions, thus resulting in a total dose of 80.5 Gy.

The selection of patients was limited to those younger than 75 years of age in reasonably good general condition (Karnofsky of 60% and above), presenting with an oropharyngeal carcinoma T_2T_3, excluding lesions arising from the base of the tongue, either N_0 or N_1 of less than 3 cm. As a matter of fact, the UICC/TNM staging system of 1979 [15] was defining N_1 as ipsilateral mobile node(s), regardless of size and number. We then decided to include only patients with either N_0 or a single node of less than 3 cm in order to keep some consistency in the selection of patients. The 1987 UICC/TNM changed the definition of N_1 in 1987 which, from this time, became in accordance with the

TABLE I

Scheme of trial EORTC 22791: hyperfractionation versus conventional fractionation in oropharyngeal carcinoma.

OROPHARYNGEAL CARCINOMA T_2T_3, N_0, $N_1 < 3$ cm M_0	RANDOMIZATION	Single daily fraction of 2 Gy 70 Gy/35 fractions/7 weeks Twice daily fractions of 1.15 Gy each 80.50 Gy/70 fractions/7 weeks

AJCC definition and with the criteria used for N_1 in this study. These selection criteria were established from the experience gathered in the pilot study in which acute toxicity appeared to be a limiting factor when more than half of the mucosa of the oral cavity was included in the target volume. In addition, the end-point of the trial being local control, we preferred to exclude patients with a low 2-year survival probability, such as patients with large or bilateral neck nodes or patients with large tumors originating from the base of tongue. Patients with limited extension to the glosso-tonsillar sulcus were eligible in the study.

Technique of radiotherapy

Treatment of the primary tumor

Cobalt-60 γ-rays and megavoltage photon beams (4–25 MV) were used with parallel opposed lateral fields to include both the primary tumor and the upper neck lymphatics bilaterally with a sufficient margin of uninvolved adjacent tissues. As a minimum, the target volume included the oropharynx from the palate to the level of the hyoid bone and posteriorly to the mid-vertebral body level. The anterior border was placed at the discretion of the radiotherapist including at least a 3 cm margin of uninvolved tissues. When extension to pharyngeal mucosa and/or clinically positive neck nodes occurred, the target volume was enlarged to the parapharyngeal lymphatics up to the base of the skull. Whenever possible, the target volume was reduced at 50 Gy. Photon beams of 10–25 MeV were recommended for the final 20–30 Gy. Brachytherapy was not allowed for boost treatment of the primary tumor. The dose to the spinal cord had to be kept as low as possible and in any case lower than 50 Gy. All fields were treated at each session in both treatment arms. The reference tumor dose was calculated at the center of the demonstrable tumor volume. Maximum and minimum doses in the target volume were also recorded [14].

Irradiation of the neck

The lymphatics included in the primary target volume covered by the parallel opposed lateral fields were of course part of the target volume and randomized between single- or twice-daily fractionation. The remaining portion of the neck (mid-jugular and supraclavicular nodes), which in all cases were clinically negative, received a single fraction per day in both arms of the study. When N_0, the lymphatics in the upper neck received a minimum dose of 50 Gy. However in most cases, the upper neck dose was much higher and N_0 subdigastric areas often received about the same dose as the primary tumor. The posterior neck was irradiated bilaterally to 50 Gy using large bilateral portals or separate electron beam strips or a combination of photons and electrons. The same techniques were used in N_1 patients to 50 Gy and a boost was then given with electron or photon beams shrinking field technique to the palpable lymph nodes up to the same dose prescribed to the primary tumor. If a residual node was palpable within 6–8 weeks after treatment completion, a local limited adenectomy was to be performed at that time.

Follow-up examinations of patients: Quality assurance

During treatment, the patients were examined at least weekly. Mucosal reaction and tumor regression were evaluated weekly and scored according to the EORTC scales for acute objective and functional mucosal reactions. Table X contains summarized definitions of these scales.

Follow-up examinations were made one month after the end of treatment, every 2 months up to 8 months and then at least twice a year with unlimited follow-up.

A quality assurance programme included site visits by a team of outside independent reviewers consisting of at least a radiation therapist and a radiation physicist. Quality control procedures included: (1) a review of forms and radiotherapy charts of randomly selected cases; (2) calibration checks of photon and electron beams, mechanical checks of the megavoltage equipment; (3) a dummy run procedure with an Alderson anatomical phantom with the same simulated clinical case (T_2T_3), asking the local participating team to follow protocol recommendations for target volume and dose calculations. The results of the centralized review and intercomparisons of this quality assurance programme were reported earlier [12,17,18].

Criteria of evaluation

The end-point of the trial was locoregional control and was assessed according to the following criteria:

- Patients were considered in locoregional control when there was no tumor discernable at clinical examination with an unlimited follow-up.
- Persistence (regardless of size) or recurrence of tumor were considered as a (local or regional) failure.
- A second primary developing within the irradiated volume was scored as a recurrence.
- Patients free of locoregional disease after salvage treatment were considered as failure of the initial treatment.

– The other criteria used in the final evaluation were disease-free survival from first day of treatment, overall gross survival from first day of treatment, acute and late complications according to EORTC/RTOG scoring scales.
Locoregional control rate was estimated by the Kaplan-Meier method as a function of time since randomization. Local and regional relapses were considered as failures on the day the relapse was observed. Patients for whom locoregional control was never achieved were considered as failures at time zero. Survival was measured from the date of randomization to the date of death (including death from all causes).

Material and methods

The trial was activated in February 1980 [8] and closed to entry at April 1987. Three hundred and fifty-six patients were accrued by 28 centers from 8 European countries (Table II). The maximum follow-up is of 11 years. The mean follow-up for living patients is longer than 200 weeks. A preliminary analysis was made in June 1990 [13]. The present detailed analysis was performed in June 1992.

Twenty-nine patients were not eligible and therefore are not evaluable. Reasons for ineligibility are listed in Table III. Follow-up is missing for 2 patients. Hence, 325 patients are included in the analysis (Table IV). The distribution and correlation between performance status and TN stage are shown in Table V. Performance status and TN stages are evenly distributed between the two arms (Tables VI and VII). A higher proportion of patients with a lower performance status (Karnofsky 60–80) is associated with positive nodes. None the less, 217 out of 323 patients (67%) had an excellent general condition (Karnofsky 90–100). The subsite of origin of the tumor in the oropharynx is equally distributed in both arms (Table VIII).

In arm 1, 10 patients (6%) received a dose lower than 70 Gy (68 or 69 Gy in 6; 58–62 Gy in 2; 42 Gy in 1; 69 Gy in 1). The two patients with lowest doses were

TABLE II

Participating centers.

Institution	Responsible radiotherapist	No. of patients	
		entered	evaluable
Centre G. F. Leclerc, Dijon	J. C. Horiot	62	60
Centre H. Becquerel, Rouen	R. Le Fur	52	51
Institut J. Godinot, Reims	T. Nguyen	37	36
Centre E. Marquis, Rennes	C. Chenal	24	20
Hôpital J. Minjoz, Besancon	S. Schraub	23	21
Hôpital Timone, Marseille	S. Alfonsi	22	19
Institute Nazionale, Milano	G. Gardani	16	15
Univ. Hospital St Rafael, Leuven	E. van der Schueren	11	11
Istitute Marie Curie, Warszawa	S. Danczak	13	10
Hôpital La Tronche, Grenoble	M. Bolla	12	11

Other participating centers (evaluable patients):
Centre J. Perrin, Clermont Ferrand (8); Areteion, Athens (7); Puerta de Hierro, Madrid (7); Hôpital Clarac, Fort de France (7); Tumor Inst., Montpellier/Hôpital, Nimes (5); Ist. F. Gentil, Lisboa (5); Univ. Hospital, Umea (5); Centre P. Strauss, Strasbourg (4); F. Bergonié, Bordeaux (4); Hôpital, Mulhouse (3); Centre A. Vautrin, Nancy (3); Tumor Inst., Rome (3); Tumor Inst., Antwerp (1); Centre L. Bérard, Lyon (1); Tumor Inst., Tilburg (1); A.M.C., Amsterdam (1).

TABLE III

Reasons of ineligibility.

Nodal status beyond N_1 or N > 3 cm	10
Surgery prior to radiotherapy	4
Older than 75 years	2
Concomitant or previous second primaries	2
Stage T_1	3
Stage T_4	1
Primary arising from the base of tongue	1
Primary located outside of the oropharynx	1
Lymphoma	2
Insufficient data to check eligibility	3
Total	29

TABLE IV

Recruitment.

PTS	Treatment		Total
	CF arm 1	HF arm 2	
Registered	176	180	356
Not eligible	16	13	29
Without follow-up	1	1	2
Analyzed	159	166	325

TABLE V

Performance status per stage.

PTS	Karnofsky		Total
	90–100	60–80	
T_2N_0	101	42 (29%)	143
T_2N_1	48	21 (30.5%)	69
T_3N_0	36	16 (31%)	52
T_3N_1	33	28 (46%)	61
Total	218	107 (33%)	325

TABLE VI

Performance status per treatment arm.

PTS	Treatment		Total
	CF arm 1	HF arm 2	
Karnofsky 90–100	103	115	217
Karnofsky 60–80	56	51	106
Analyzed	159	166	325

TABLE VII

T-N distribution per treatment arm.

T-N	Treatment		Total
	CF arm 1	HF arm 2	
T_2N_0	73	70	142
T_2N_1	31	38	69
T_3N_0	22	30	52
T_3N_1	33	28	61
Analyzed	159	166	325

not analyzed for locoregional control and were evaluated for acute tolerance and survival.

In arm 2, 22 patients (12%) received a dose lower than 80 Gy. This dose was of 75–79.70 Gy in 12 cases; between 64 and 74 Gy in 8; 55 Gy in 1; and 36.80 Gy in 1. The two patients with lowest doses were not analyzed for locoregional control and were only evaluable for acute tolerance and survival.

The actual median and mean doses delivered and the actual median and mean overall treatment time are shown in Table IX.

TABLE VIII

Oropharyngeal subsites per treatment arm.

Subsites	Treatment		Total
	CF arm 1	HF arm 2	
Tonsillar	76	77	153
Soft palate	25	37	62
Anterior pillar	26	18	44
Glosso-tonsillar	13	15	28
Lingual-epiglot.	9	12	21
Posterior pillar	9	5	14
Lat. wall pharynx	1	2	3
Analyzed	159	166	325

TABLE IX

Dose/time variations.

	Actual reference dose (Gy) to the primary tumor per treatment arm		
	median	mean	S.D.
Arm 1	70	69.7	5.8
Arm 2	80.5	79.4	4.6
	Actual overall treatment time (days) per treatment arm		
	median	mean	S.D.
Arm 1	51	53.3	7
Arm 2	51	52.6	9.5

Results

Acute tolerance

Three hundred and twenty eligible patients are evaluable for acute side effects. Table X summarizes the objective and functional mucosal reactions recorded and scored during treatment.

Objective acute mucosal reactions were more severe in arm 2 ($p = 0.01$). Overall, functional mucosal reactions led to a treatment interruption in 6% of the cases (4.5% in arm 1 vs. 7.5% in arm 2). In summary, more

TABLE X

Acute side effects.

	Treatment		Total
	CF arm	HF arm	
Total	159	166	325
Inevaluable	1	4	5
Total	158	162	320
Objective mucosal reactions:			
None	1	–	1
G_1: mild mucositis	13 (8%)	7 (4.5%)	20
G_2: patchy mucositis	66 (42%)	47 (29%)	113
G_3: diffuse mucositis	78 (49%)	108 (66.5%)	186
Functional mucosal reactions:			
None	1	2	3
G_1: mild irritation	21 (13%)	13 (8%)	34
G_2: moderate irritation	72 (45.5%)	73 (45%)	145
G_3: liquid diet only	47 (30%)	48 (30%)	95
G_4: oral alim. impossible	17 (11%)	26 (16%)	43
Stopped <70 Gy	7 (4.5%)		
Stopped <80 Gy		12 (7.5%)	

TABLE XI

Late side effects.

	Treatment		Total
	CF arm	HF arm	
Evaluable cases	118	135	253
Grade 2, 3 fibrosis	21	22	43
Grade 2, 3 mucosal necrosis	7	12	19
Grade 2, 3 edema	15	21	36

severe acute mucosal reactions occurred in arm 2, which did not alter the feasibility of the proposed scheme: 93% of patients entered in arm 2 received at least 95% of the prescribed 80.5 Gy to the primary tumor.

Late side effects

These were observed and scored in all patients and were analyzed in patients in locoregional control (253 evaluable cases). There are more evaluable patients in arm 2 as a consequence of a higher locoregional control rate. Table XI shows the distribution per type of complication, per arm, per grade 2, 3 events. These figures are not interpretable as such, since several events may occur in the same patient. Hence the evaluation of complications was performed using the Kaplan-Meier method for each type of complication. This also eliminates the bias of differences in disease-free follow-up time. The curves of the 2 arms are nearly superimposed for all complications and grades (Fig. 1), for late damage to mucosa, bone, fibrosis, and edema (either laryngeal or soft tissues of the neck). The two curves deteriorate with time of observation, about 50% of patients being free of grade 2 and 3 complications at 5 years. The evaluation of long-term effects to connective tissue is of prime interest since the dose received by subcutaneous normal tissues of the upper neck area is often greater than the dose prescribed to the primary tumor. Cobalt-60 beams were used in most cases up to 50 Gy and sometimes throughout the whole treatment, resulting in maximum doses in the 85–88 Gy range in arm 2 and 74–77 Gy range in arm 1. Figure 2 shows that there is no significant difference in the actuarial incidence of grade 2, 3 fibrosis between treatment arms. No grade 2, 3 neurological complications were observed. The dose delivered to the spinal cord was equal to or less than 50 Gy.

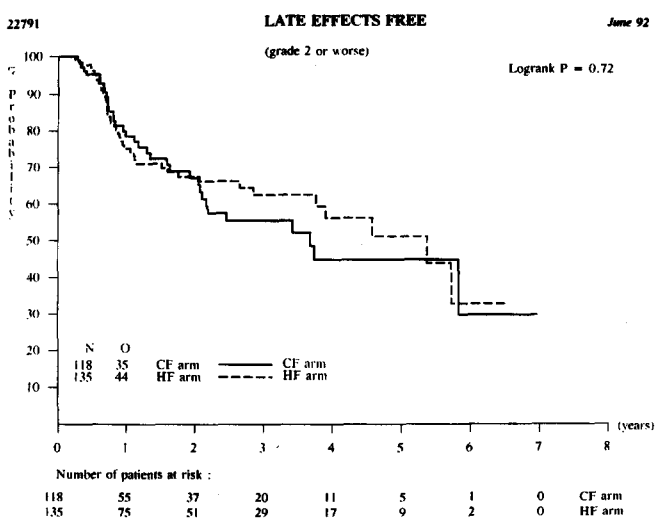

Fig. 1. Actuarial estimate of patients free from grade 2, 3 late side effects per treatment arm (CF, conventional fractionation; HF, hyperfractionated).

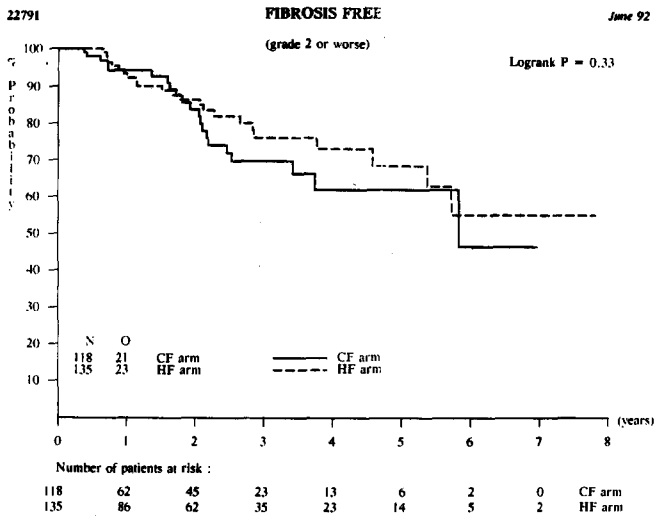

Fig. 2. Actuarial estimate of patients free from grade 2, 3 fibrosis per treatment arm.

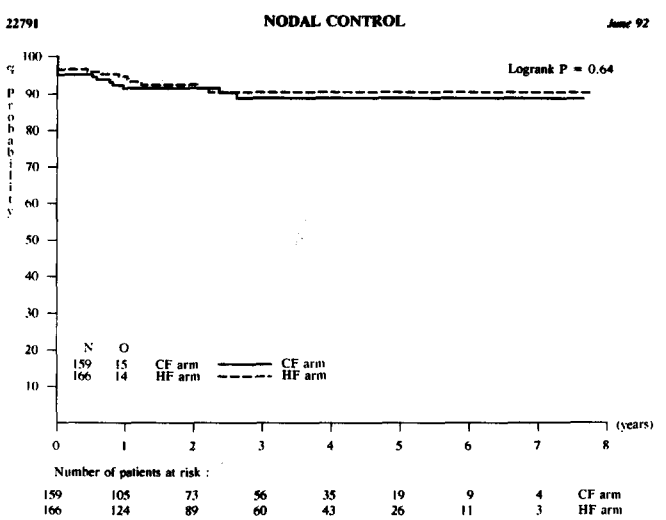

Fig. 3. Probability of control of regional nodes per treatment arm.

Locoregional control

Control of nodes (Fig. 3)

Control of the nodes was not achieved in 29/325 cases (9%). At 5 years, 93% of the N_0 and 90% of the N_1 patients remained nodal disease-free. No difference was observed between therapy arms. These data are not surprising since a high regional control rate was expected with the strategy and doses of radiotherapy alone used in both arms for N_0, $N_1 < 3$ cm cases [1,5,9,10]. Also, a similar regional control in both arms was a prerequisite to ensure that any difference observed in local control resulted only from differences in treatment to the primary tumor and not from an effect of differences in regional control on the probability of control of the primary tumor. Nine patients (3%; 5 in arm 2, 4 in arm 1) had adenectomies or modified upper neck dissection performed within 6–8 weeks after completion of radiotherapy. Residual disease was identified in 3 cases. These 3 patients were not considered as nodal failures since this treatment sequence was part of the initial treatment strategy and complied with protocol recommendations in case of doubtful clinical funding at the end of radiotherapy. None of these 10 patients presented later with a nodal failure nor developed acute and/or late neck complication.

Locoregional control

Overall, combining the 2 arms, the 5-year locoregional control rate was 47%. Of the 53% of patients without locoregional control at 5 years, 14% had uncontrolled disease at the end of treatment, 28% relapsed during the first 2 years and 11% after the second year.

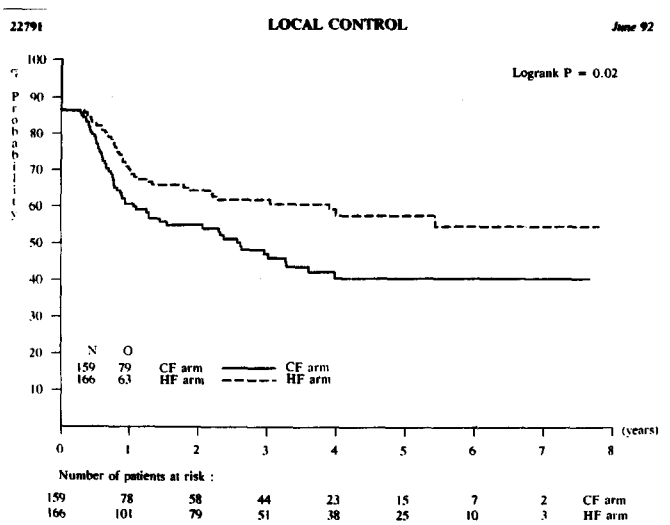

Fig. 4. Probability of locoregional control per treatment arm: all patients.

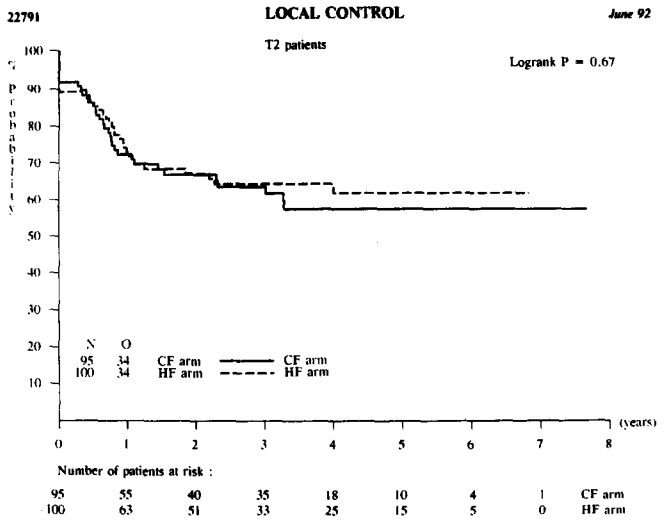

Fig. 5. Probability of locoregional control per treatment arm: T_2 patients.

Local control versus treatment arm

Local control (Fig. 4) is significantly higher ($p = 0.02$) in arm 2 (hyperfractionation) than in arm 1 (single fraction per day) resulting in a 5-year local control of 59% vs. 40%. This advantage is even larger ($p < 0.003$) in the 218 patients with a good initial performance status (Karnofsky index of 90–100). It is also significantly improved in the hyperfractionated arm for patients staged T_3N_0 ($p = 0.03$), T_3N_1 ($p = 0.01$), T_3 ($p = 0.001$, Fig. 6) but not for T_2 ($p = 0.67$, Fig. 5).

Survival (Fig. 7)

Locoregional control was the end-point of the trial. However, the improvement in locoregional control re-

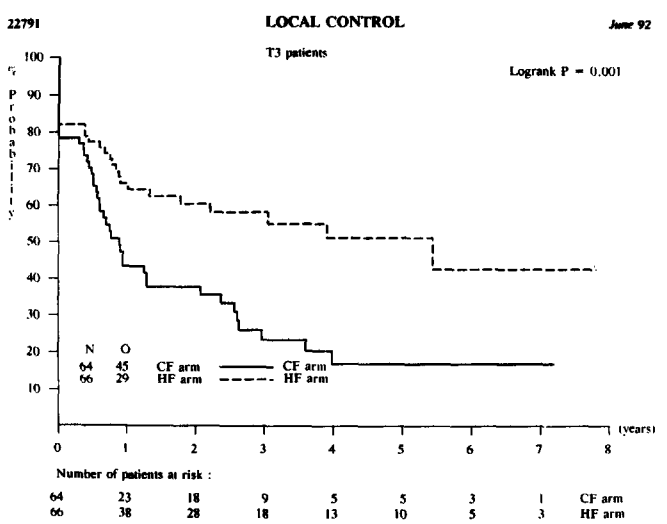

Fig. 6. Probability of locoregional control per treatment arm: T_3 patients.

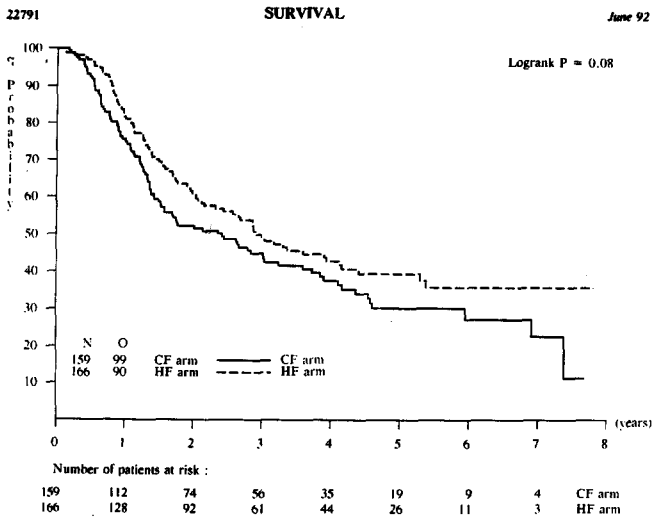

Fig. 7. Probability of survival per treatment arm.

sulted in an improved survival that was not quite significant at the 5% level ($p = 0.08$) in patients receiving HF.

Prognostic factors

The following variables were investigated as potential prognostic factors of locoregional control and survival: T and N classification, tumor and nodal volume, histology, tumor origin, performance status and age. Firstly, the influence of these factors on survival and locoregional control rate was estimated by univariate analysis, using the Kaplan-Meier estimate within subgroups and the log-rank test for comparison. All these factors have been further analyzed in multivariate Cox regression models to determine a set of independently significant prognostic factors and to estimate the effect of treatment after adjustment for these factors.

Univariate analysis

The T-N stage was correlated with the probability of locoregional failures at a high significance level ($p = 0.004$) with an increasing failure rate in the following orderly stage sequence: T_2N_1, T_2N_0, T_3N_0, T_3N_1.

Locoregional control rate was found to be significantly higher for tumors with small volume and in old patients; survival was found to be significantly worse in T_3N_1 patients, in poorer performance status patients and in patients with undifferentiated tumors.

Multivariate analysis

All these potential prognostic factors have been investigated in a Cox regression analysis to determine a set of independently significant prognostic factors of locoregional control and survival. For locoregional control, the only independently significant prognostic factors are the T classification and the treatment arm; significance levels are given in Table XII. As to the survival, performance status and N staging are the only independent prognostic factors; treatment arm affects survival after adjustment for these two factors but not at a conventionally significant level; significance levels are given in Table XIII.

TABLE XII

Prognostic factors for locoregional control.

Factor	*p*-value
T-classification	0.0004
Treatment arm	0.0072

TABLE XIII

Prognostic factors of survival.

Factor	*p*-value
Performance status	0.004
N-Classification	0.036
(treatment)	0.064 (n.s.)

Discussion

Although the advantage of hyperfractionation in the radiotherapy of head and neck carcinoma has been suggested by several authors, there has not yet been a report of a controlled clinical trial to support this finding. Most studies reported to date were either phase I, II trials, and when randomized, had no control arm with conventional fractionation.

The first pilot study was performed at Houston [20]. Then a small group of patients was treated in a similar manner at Dijon and reported by Jampolis [16]. This subset became the core of the larger pilot study of 103 patients [11] which was summarized in the introduction of this paper.

Million and Parsons [19] used a similar hyperfractionation scheme as in protocol 22791 with doses ranging from 74.40 to 81.60 Gy. There were no significant improvement in local control rates for T_2–N_3 tonsillar region or soft palate tumors compared to historical controls treated once per day. There was no increase in local control rate with escalation of dose from 74.40 to 81 Gy, but there was an increase in complications with increasing dose. Update on this material through March 1991 still fails to show any improvement in local control for the tonsillar region or soft palate compared to daily fractionation. They have noted, however, significant improvements in local control for the larynx

and hypopharynx in the hyperfractionation group compared to historical controls.

Finally, a large prospective randomized multi-institutional trial (phase I late effects/II) of hyperfractionation was conducted by the RTOG from 1983 to 1987 and accrued 447 patients in 4 escalating dose levels without a control arm with conventional fractionation.

In the present EORTC trial, several factors deserve further comments and raise new questions:

T stage. The improvement in locoregional control using hyperfractionation was mostly observed in patients with larger tumors (T_3) regardless of nodal stage (N_0 or N_1). This is not surprising since locoregional control rates obtained by conventional regimes are already quite high for T_2, hence making further improvement more difficult to demonstrate than for T_3.

Timing of locoregional failures. The difference between the two treatment arms is already observed after 2 years and does not increase very much thereafter: 13% of the failures occur after 2 years in arm 1, and 10% in arm 2.

The interval between fractions and late tissue damage. A minimum interval of 4 h was respected in all patients. In 1984–85, suggestions came from radiobiologists (R. Withers, J. Fowler) that a significant amount of recovery of sublethal damage was still occurring 4 h after the first fraction. We then recommended to trial participants to treat their patients with the maximum interval between daily fraction which was consistent with practical schedules. Overall, it can be assumed that about 80% of patients entered in this trial had an interfraction interval of only 4–6 h. An analysis of late complications correlated to the interval between fractions was not feasible since the difference between 4 and 8 h was not thought to be of a high relevance in the early 1980s and was not recorded in the treatment forms. This "less than optimal" interfraction time in our study, gives some additional weight to the observation that 80.5 Gy did not result in more late tissue damage than 70 Gy. The overall treatment time being the same in the two arms (7 weeks), the only different parameter was the number of fractions per day. It can then be assumed that a minimum interval of 4 h between the two fractions was sufficient to allow the repair of sublethal damage to mucosa, bone and connective tissues for a maximum total dose of 80.5 Gy delivered in 7 weeks and 70 fractions. However it is possible that using a longer gap during 2 fractions per day (e.g. 8–12 h) should result in a lower incidence and severity of late morbidity and possibly less severe acute morbidity. As a matter of fact, although not significant, a trend to a lesser damage is observed between 3 and 5 years in the hyperfractionated arm (Figs. 1 and 2). The relevance of the interfraction interval has now been clearly demonstrated by Cox et al. [6,7] in the RTOG escalating dose trial. A significant decrease of grade 3 + acute effects and of grade 4 + late effects was observed with interfraction intervals larger than 4.5 h as compared to equal or less than 4.5 h. The authors concluded that sparing of normal tissues with an improved therapeutic gradient would result from high total doses given as 2 fractions per day. Their data support the comparison of 81.6 Gy using hyperfractionation with a standard fractionation control arm, exactly what was used in the EORTC protocol 22791.

Why was a better locoregional control achieved in arm 2? Beyond the statistical evidence for a better clinical result, it is of interest to perform a critical review of the radiobiological rationale for these results. Was it only due to the extra 10.5 Gy delivered in arm 2 in the same overall treatment time? Would it then be only dose dependent? Because the biologically effective dose to the tumor is enhanced more by HF than is the biologically effective dose to late responding normal tissues, the effective dose rate per week is also increased. The acceleration of tumor dose rate is also about the 1.1 factor calculated earlier for the increase in therapeutic ratio, whereas there is not much acceleration in dose rate to late responding normal tissues. It is therefore possible that the observed advantage of pure HF over CF may result from a favorable combination of several radiobiological reasons. Future trials should address this essential question by exploring the individual patient tumor cell kinetics in fractionation trials. The results of this trial together with radiobiological data [3,4] would support the rationale for submitting tumors with long potential doubling times (T_{pot}) to pure HF regimes and tumors with short T_{pot} values to AF regimes, or to the combination of both AF and HF.

Why did patients with a lower Karnofsky status (60–80) have no benefit from hyperfractionation?
This is indeed a frustrating observation since a 60–80 Karnofsky status would often be considered as being quite satisfactory in most patients with head and neck cancers. The analysis did not demonstrate any difference in distribution of overall treatment times nor in total doses between the two Karnofsky groups. As stated before, there was a non-significant increase of N_1 cases in the group of patients with a 60–80 Karnofsky index. Unfortunately, the hemoglobin level was not re-

corded in this study; this may also play a role since the hemoglobin level is more likely to be lower in the group with a lower Karnofsky status. Also, they represented a smaller subgroup (107 patients) than the patients with 90–100 Karnofsky index (218 patients) making it more difficult to detect any significant difference. Their probability of dying sooner from intercurrent disease is also higher. All these facts may contribute to explain the absence of measurable benefit from hyperfractionation in this group. This, again, stresses the importance in future trials of stratifying patients according to the performance scale and to aim at very large accruals (300–500 patients) when patients in moderately good general condition (Karnofsky 60–80, WHO 2) are entered in trials of curative treatment of head and neck cancers.

Conclusion

This trial confirms the improvement of locoregional control when dose is increased to 80 Gy in a twice per day hyperfractionated regimen for T_2T_3 oropharyngeal carcinoma, N_0, $N_1 < 3$ cm. Such an increase in dose, when delivered as a classical regimen, using a single fraction of 1.8–2 Gy per day would be associated with an increased risk of severe acute and late complications. The present trial brings clinical evidence to support the radiobiological predictions that delivering the dose with 2 fractions per day would allow an increase of total dose from 70 to 80.5 Gy without increasing the late complication rate. The hyperfractionated regime (80.5 Gy in 70 fractions and 7 weeks) was followed by a higher local control ($p = 0.02$) than with the conventional fractionation regime of 70 Gy in 35 fractions and 7 weeks. Patients with the best general condition (Karnofsky 90–100) are the main beneficiaries of this increase in therapeutic effect. This obviously does not solve the problem of local control for all sites of head and neck cancers. However, it emphasizes the major interest of modified radiotherapy regimes based upon radiobiological concepts. This trial was also of value to point out which patients should be treated routinely with hyperfractionation, and to provide some suggestions on which parameters should be addressed in future clinical trials exploring variations in fractionation and overall treatment time in radiotherapy.

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