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TOLERANCE TO ACCELERATED FRACTIONATION IN THE HEAD AND NECK REGION

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To improve efficacy of radiotherapy in head and neck carcinomas, shortening the treatment time by accelerated fractionation is one possible method. However, there is a risk of enhancing side-effects. To study the tolerance to accelerated fractionation a study was thus performed where 2.0 Gy/fraction was given twice daily with 7–8 h interval between fractions. The total dose was 60 Gy and the overall treatment time 19–22 days. Thirteen patients with tumours in the head and neck region were consecutively included in the study. The treatment volumes ranged from encompassing the primary tumour with a margin to including the oral cavity and neck nodes bilaterally. Evaluation has been done by means of scoring the mucosal reactions, subjective estimation of pain, and functional impairment. Furthermore, the late radiation effects have been assessed by scoring of telangectasia, fibrosis of subcutaneous tissues and necrosis. The median follow-up time was 37 months. The treatment was generally well tolerated and could be completed without interruptions. However, in most cases the acute mucosal reactions appeared to be severe for a longer time than after standard fractionation. Restitution of normal mucosa without persistent complications has been achieved in all cases. The toxicity of this treatment schedule seems to be acceptable. No severe late complications have occurred during the follow-up period. A comparison with other treatment schedules has been made, using the linear-quadratic (LQ) model to calculate biologically effective dose (BED). In the present schedule it is shown that the early reacting normal tissue and tumour effects are predicted to be similar to the EORTC schedule whereas the late effects would be less pronounced. The CHART protocol gives less effects on early responding tissues due to the low total dose.

Ever since the first published result by Strandqvist (1) on the correlation between overall treatment time, number of fractions and the total dose, numerous different fractionation schemes have been the subject of clinical trials (2, 3). By estimating the kinetics of proliferation in tumours in the clinical setting (4) it has been shown that many tumours have a potential tumour doubling time (T_{pot}) shorter than 5 days (5). For squamous cell carcinomas of the head and neck region an average T_{pot} of 4.5 days using flow cytometry and of 2.4 days combining histological assessment with flow cytometry, have been found (6). This may indicate that a decreased overall treatment time, i.e. accelerated fractionation, could give a therapeutic gain.

Hitherto, most clinical studies on acclerated fractionation have used fractionation schemes that combine accelerated fractionation with hyperfractionation (7) or have included a 'gap' during which tumour repopulation might occur (8). Data on purely accelerated radiotherapy (i.e. where the dose per fraction is kept at 2 Gy) are sparse. However, there are some data on accelerated radiotherapy in the head and neck region, e.g. Lamb et al. (9) who used three fractions of 1.8 Gy, with 4-h intervals, 3 days/week to a total dose of 59.4 Gy in 24–25 days. The treatment was considered to be toxic resulting in some deaths due to acute toxicity. Furthermore, Olmi et al. (10) used 3

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fractions/day with a 4-h gap, 4–5 days per week to a total dose of 48–52 Gy in 11–12 days. The treatment led to a high proportion (24%) of patients with severe late sequelae. Therefore, in this first study the aim was to evaluate the toxicity of accelerated fractionation where 2.0 Gy/fraction was given twice daily, 7–8 h apart to a total dose of 60 Gy. Moreover, a comparison with other schedules, e.g. CHART and EORTC 22851, was performed by means of the linear quadratic model (7, 8, 11).

Material and Methods

Selection of patients. Fourteen patients with tumours ranging from early small tumours to locally advanced ones were consecutively included in the study. The criterion on inclusion was a substantial amount of mucous membranes included in the target volume. Thirteen of the patients could be evaluated. One patient with advanced sarcoma of the floor of mouth, and a poor performance status prior to treatment, died shortly after treatment due to pulmonary embolism. The death was not considered to be treatment-related. The sex, age, site of tumour, and TNM-classification of the patients are shown in Table 1.

Radiotherapy. Patients were treated twice daily with 2.0 Gy/fraction, 5 days/week. The interval between the two daily fractions was 7–8 h. The total dose was 60 Gy and the overall treatment time 19–22 days. Treatment was given with 4–6 MV x-rays from a linear accelerator and in some cases with additional electrons from a 20.9 MeV microtron for posterior neck node treatment. Absorbed doses were specified according to the recommendations of ICRU (12). Typical planning target volumes and field arrangements are shown in Fig. 1. Additionally, 4 patients received treatment from opposed fields covering a larger

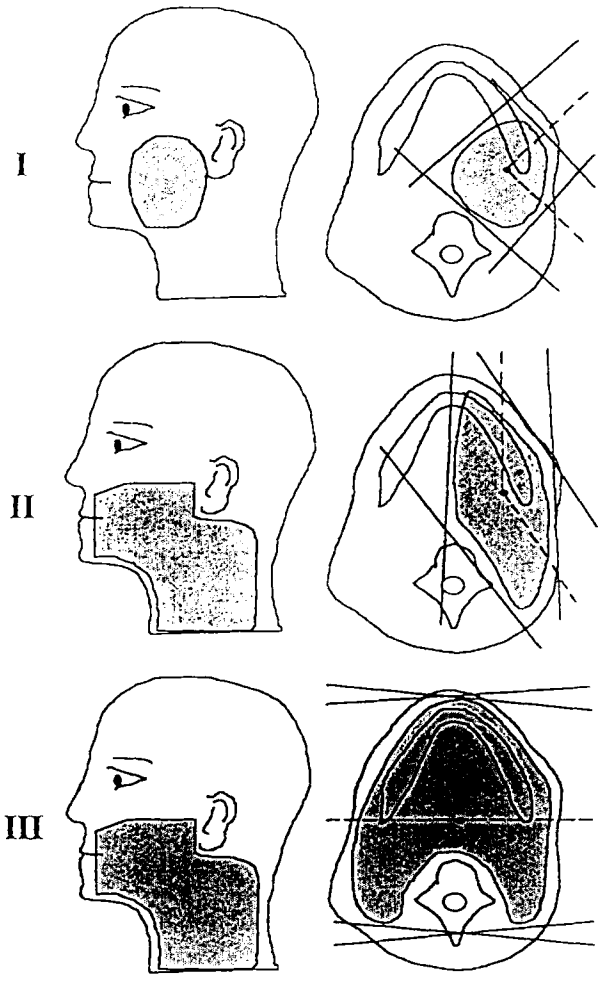

Fig. 1. The projected treatment volume and field arrangement for typical cases with a small (I), moderate (II), and large treatment volume (III).

Table 1

Patient material, radiation fields, and tumour response

Sex	Age	Tumour site	TNM	Field size width × length (cm)	Field arrangement	Follow-up (months)	Local recurrence (months)
F	67	Soft palate	T1 N0 M0	7.5 × 9.5	II	48	–
F	56	Tonsil	T1 N1 M0	8.5 × 14.0(7.5)	II	48	–
F	76	Parotid gland	T3 N0 M0	7.0 × 10.0	I	43	–
F	76	Gingiva	T4 N0 M1	10.0 × 10.0	II	43*	–
M	74	Parotid gland	T2 N0 M0	6.0 × 9.5	I	41	–
F	83	Tonsil	T2 N0 M0	9.5 × 10.5	II	38	–
M	63	Nasal	-§ N0 M0	5.0 × 5.5	I	37	–
M	81	Nasal	-§ N0 M0	6.0 × 5.0	I	34	12
M	82	Floor of mouth	T2 N1 M0	15.0 × 9.0	III	30	–
F	63	Floor of mouth	T1 N1 M0	10.0(6.0) × 9.5(6.0)	III	27	–
F	77	Tonsil	T1 N0 M0	6.5 × 7.5	I	27	–
M	63	Tongue	T4 N1 M0	15.5 × 13.5	III	27**	9
M	70	Gingiva	T4 N0 M0	11.5(5.0) × 7.5(6.0)	III	26	–

Figures in brackets denote the size after reduction of treatment volume after 46 Gy. Field arrangement, I, II, and III corresponds to the numbers in Fig. 1. *Dead in distant metastases at 5 months, with local control. **Dead at 12 months with local recurrence. §T stage not defined for nasal carcinomas.

volume. Details on field sizes and techniques are given in Table 1. Shrinking field technique was used in cases where prophylactic irradiation was given to the lymphnodes. In such cases the prophylactic dose was 46 Gy. The dose to the spinal cord was kept below 40 Gy in all cases. Special attention was given to dental care and adequate hygiene of the oral cavity, before, during and after treatment. All patients received sucralfate (Andapsin) for mouth swishing, during the treatment and two weeks thereafter in an attempt to decrease the mucosal reaction. This was based on results from our department which showed protection against mucosal reaction in the intestine (13).

Scoring of the acute effects. Assessment of side-effects was done weekly during the course of radiotherapy. After the treatment the reactions were assessed at 2, 4, and 6 weeks and then with 4–5 weeks interval until 6 months, thereafter every 2–3 months. At each visit the mucosal reaction was scored by the physician. Furthermore a subjective estimation of pain, and functional impairment was done by the patient. On each occasion a questionnaire was completed and photos were taken. The scoring system is shown in Table 2.

Table 2

Scoring system used to evaluate early and late normal tissue effects

Early reactions
- Epithelitis
  - 0 = No reaction
  - 1 = Redness
  - 2 = Redness and small areas of desquamation
  - 3 = Confluent epithelial desquamation
- Pain
  - 0 = No pain
  - 1 = Mild
  - 2 = Moderate
  - 3 = Severe
- Functional impairment
  - 0 = None
  - 1 = Able to eat all kinds of food with slight difficulty
  - 2 = Able to swallow only liquid or semi-solid food
  - 3 = Needs tube feeding

Late reactions
- Mucosal atrophy
  - 0 = None
  - 1 = Slight thinning of mucosal membranes
  - 2 = Pronounced thinning of mucosal membranes in small areas ($<4\ cm^2$)
  - 3 = Pronounced thinning of mucosal membranes in larger areas
- Telangiectasia of mucous membranes
  - 0 = None
  - 1 = Number of telangiectasias < 5
  - 2 = Number of telangiectasias 5–15
  - 3 = Number of telangiectasias > 15
- Induration of subcutaneous tissues
  - 0 = None
  - 1 = Slight induration
  - 2 = Moderate induration, but no restriction in movements
  - 3 = Restriction of movements
- Ulceration or necrosis
  - 0 = None
  - 1 = Present

Scoring of late effects. Assessments of late radiation effects were carried out every 2–3 months. The atrophy and telangiectasia of mucous membranes were assessed, as well as ulceration or necrosis, by a simple, arbitrary score shown in Table 2.

Comparison of different fractionation schemes. For comparing predicted early and tumour effects from different fractionation schemes the BED (biologically effective dose) has been calculated from the linear-quadratic model with a time factor to allow for proliferation. The model for tumour and early reacting normal tissue has the form given by Fowler (11)

$$BED = E/\alpha = nd(1 + d/\alpha/\beta) - \ln 2(T - T_k)/\alpha T_p \quad [Eq.\ 1]$$

where E is the total effect, α and β are the linear and quadratic coefficients for radiation cell death, n is the number of fractions, d is the dose per fraction, T is the overall treatment time, T_k is the time from start of treatment to start of (accelerated) cell proliferation and T_p is the average doubling time of the tumourigenic or tissue rescuing cells, after treatment has started.

For late effects the LQ-model without the time factor was used

$$BED = E/\alpha = nd(1 + d/\alpha/\beta) \quad [Eq.\ 2]$$

The following radiotherapy schedules have been analysed in the theoretical comparison:
- Standard: 1 fraction/day, 2 Gy/fraction, 33 fractions/6.5 weeks, total dose 66 Gy.
- CHART: 3 fractions/day, 1.5 Gy/fraction, 36 fractions/12 days, total dose 54 Gy (7).
- EORTC 22851: 3 fractions/day, 1.6 Gy/fraction, 45 fractions/5 weeks, total dose 72 Gy. The schedule also includes a gap of 12–14 days after 8 days of treatment (8).

Results

Follow-up varied between 27 and 48 months (median 37 months). The evaluation of side-effects is shown in Fig. 2 where the proportions reaching score 2 and 3 are shown. The pattern of appearance and resolution are similar for mucosal reaction, pain and functional impairment. The treatment was generally well tolerated. The acute reactions started during the first week of irradiation. Most patients reached the peak reaction in the second week, some during the third though. The first signs of recovery could be observed four weeks after start of radiotherapy. The duration of reactions was influenced by the treated volume. Two patients needed tube feeding during or after therapy. In both cases the tube feeding could be stopped within two weeks. Skin reactions did not seem to be more severe than with standard treatment. Even in the two cases of nasal

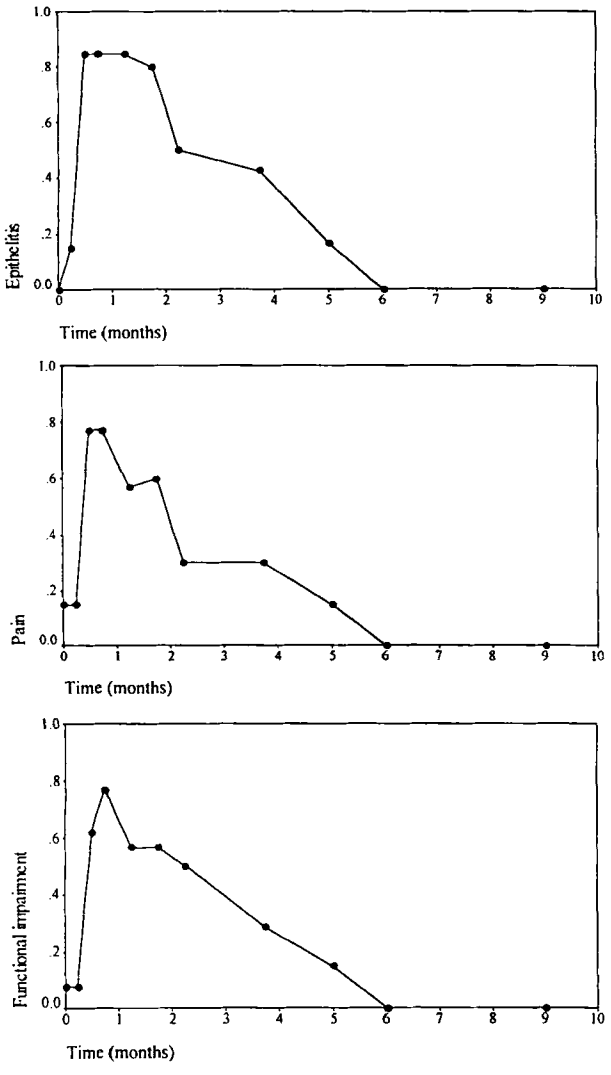

Fig. 2. The proportion of patients with side-effects of grade ≥ 2 versus time after start of treatment.

carcinoma, where moist desquamation of the skin occurred because of exceptionally high skin-dose due to use of bolus material, the reaction resolved within two months after completion of therapy. Complete restitution of the acute reactions was achieved in all cases. However, one case had a persistent mucosal ulceration of about 1 cm^2 for 5 months before it was healed.

Concerning late reactions, only slight to moderate reactions have been noticed, so far (Table 3). In one case, subjected to surgery following radiotherapy, a gingival ulceration, without signs of osteonecrosis or subjective distress was observed for 23 months postoperatively. Eventually, the ulceration healed after long-term antibiotic therapy.

In all patients a complete regression of the primary tumour and of all lymph node metastases was encountered. Only two patients had a local recurrence. One patient with a nasal carcinoma recurred locally after 10 months and is free of disease after salvage surgery. The other patient, with an advanced carcinoma of the tongue, had locally recurrent disease after 9 months and died three months later of uncontrolled local disease.

Table 3

Distribution of late effects among the patients at the last follow-up

Grade	0	1	2	3
Mucosal atrophy	8	3	2	0
Telangiectasia	11	2	0	0
Induration of subcutis	9	4	0	0
Ulceration/ necrosis	12	1*	–	–

* complication after combined treatment

Discussion

In the present accelerated radiotherapy schedule the patients tolerated the treatment fairly well and the planned radiotherapy sessions could be completed. However, the acute reactions appeared to be more severe and of longer duration than is usually encountered with standard fractionation. The importance of prophylactic support, including adequate nutrition of the patient and locally applied radioprotective substances is more important than with conventional regimens. In contrast to the suggestions of earlier studies (9) the acute reactions seem to be quite tolerable even when quite large volumes are treated. One explanation for this may be the longer interfraction interval used in this study, 7–8 h, compared to 4 h in the other studies (9, 10).

The observed long-standing epithelial reaction may increase the risk of consequential late effects. However, no severe late radiation effects were observed in any patient. One patient with a mucosal defect persisting a long time after surgery suggests that wound healing might be impaired. Noteworthy, 5/13 patients had surgery in the irradiated volume and only one of these displayed delayed wound healing. Thus, the general impression is that the late reactions are not more pronounced than after conventional treatment, but further consecutive comparative studies between conventional and accelerated fractionation are of importance. One way of comparing different treatment schedules is to use a mathematical model. The predictions of early and late effects in normal tissues as well as tumour effect for a selection of treatment schedules, using calculation of BED, are shown in Fig. 3. In the given examples the values of α/β and α are chosen as representative from an overview of published data (11). Concerning the length of time before accelerated repopulation starts in tumours (T_k) there are diverging suggestions, from 'a few days' (11), to 3–4 weeks (14). However, if the T_k is as long as 4 weeks, only marginal effects from reducing overall treat-

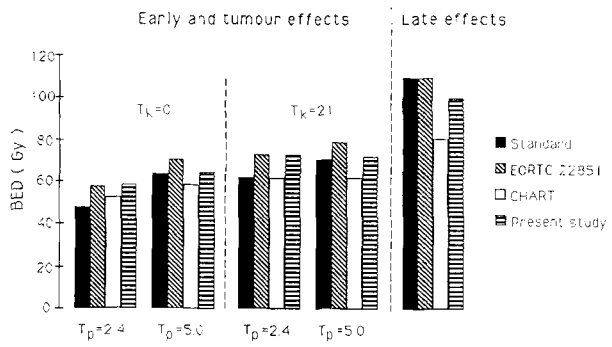

Fig. 3. BED for tumour/early reacting normal tissue and late effects for some selected radiotherapy schedules. α is assumed to be 0.4 Gy^{-1}. α/β is assumed to be 10 Gy for early and tumour effects, and 3 Gy for late effects. No corrections for incomplete repair are made.

ment times are to be expected. Therefore, we have chosen the extreme low end (zero) and 21 days for illustration. Estimates of T_k for early reacting normal human tissues seems to be covered by the range proposed for tumours (15). In the calculations of the time factor, only positive values of $(T - T_k)$ are allowed and all the others are denoted zero since otherwise we would adopt a concept of negative proliferation. The T_p are chosen from the pretreatment average T_{pot} (2.4 days) in head and neck cancers, measured by combined histological and flow cytometric analysis (6). The other value, 5 days, is arbitrarily chosen for illustrating less rapidly but clinically plausible proliferating tumours. It is noteworthy that the pattern of the calculated tumour effects differ only moderately when different kinetic parameters are assumed. It was only for the most rapidly proliferating tumours with the shorter T_k that the standard treatment showed a pronounced drop in BED. The EORTC and the presently studied schedules are predicted to have similar effects on rapidly proliferating tissues whereas the EORTC schedule displays a more pronounced effect on the less rapidly proliferating tissue. Nevertheless, as a consquence of the treatment interval, which may allow accelerated repopulation, the EORTC schedule has the greatest effect on the least rapidly proliferating tumours and normal tissues. In contrast, both CHART and the purely accelerated regimens soon reach their maximum BED, making them less sensitive to different kinetic parameters. This insensitivity is most pronounced for CHART which, however, never reaches BED > 62 Gy due to the low total dose, which can be disadvantageous in certain situations.

CHART is predicted to result in most sparing of late reacting normal tissues. EORTC and the standard schedules induce the same late effects, whereas the treatment used in this study is predicted to give a 10% lower effect on late reacting tissues. Thus, in most situations the accelerated fractionation scheme would give at least as good a tumour effect as the CHART or EORTC protocols. However, the calculations should be regarded with great caution since the model is not yet proven to be valid and the tissue parameters used are not known in detail for all tissues. Furthermore, there is evidence of the model sometimes underestimating late effects (16).

Both the CHART and the EORTC trials are designed to avoid treatment during the maximal acute epithelial reaction. The CHART treatment is completed before the reaction starts and in EORTC, a 12–14 days split is used after 8 days of treatment. In our opinion, there seems to be no major disadvantage in treating during maximal epithelitis since no treatment interruption was needed in any patient. The responses of early reacting normal tissues and many tumours to changes in time, dose and fractionation are similar (i.e. high α/β-ratio, short T_p, and a T_k that may be shorter than the standard overall treatment time). This indicates that regimens designed deliberately to give sparing of the mucosa may lead to a risk of sparing the tumour. The aim of the radiotherapy should perhaps be to induce the highest tolerable degree of acute reaction while concomitantly avoiding the risk of late damage.

In conclusion, the acute toxicity of this treatment schedule seems to be tolerable. As predicted, the acute effects seem to be more intense and prolonged compared to standard treatment. BED for rapidly proliferating tissues are similar or higher for the used fractionation scheme than the accelerated and hyperfractionated schedules used in the EORTC and CHART trials, and standard fractionation. The main objections against CHART and the EORTC protocol (i.e. the low total dose and the treatment gap respectively) are dealt with, by the purely accelerated schedule. The late effects are predicted to be reduced in comparison to standard and EORTC schedules but more severe than in CHART, which is not contradicted by the results of this study. The schedule is easy to perform since no reorganization of the radiotherapy department is needed as the treatment can be given during regular working hours. Further studies are certainly justified to evaluate any therapeutic benefits from this treatment.

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