ESCALATED HYPERFRACTIONATION IN RADIOTHERAPY FOR HEAD AND NECK CANCER – 5-YEAR RESULTS

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ABSTRACT

Purpose: To evaluate 5-year results of escalated hyperfractionation schedule in aspect of local tumour control (LTC) and late radiation toxicity.
Material and methods: Forty eight patients with squamous cell carcinoma of oral cavity (34 pts), oropharynx (11 pts) and larynx (3) in stage T1-4N0-1 have been treated at Centre of Oncology in Gliwice, between the years 1988-92. There were four patients with T1 primary tumour, 27 with T2, 11 with T3 and 2 with T4; in 4 patients the tumour stage remains unknown (TX). All the patients were treated by radiation therapy alone, using the technique of two opposed parallel fields and hyperfractionation with escalation of the dose per fraction during the second part of the treatment schedule. The total dose ranged between 62,2 and 74 Gy. The median follow-up was 62 months.
Results: Despite of the relative high proportion of complete local regressions (75%), the 5-year LTC rate of 54% was noted in the whole group of patients. Stage-related LTC rates were as follows: 100% for TX tumours, 50% for T1, 55% for T2, 45% for T3 and 0% for T4. Acute radiation reactions were more intensive than those usually observed during conventional radiotherapy; all patients experienced a confluent mucositis and two waves of acute mucosal reaction because of treatment gap were observed during the radiation course. Severe late radiation toxicity (grade IV) was noted in two patients (4%).
Conclusions: Long-term tumour control results of escalated hyperfractionation radiotherapy may suggest that there is no benefit of a such regimen. However, in the majority of patients the treatment course differed markedly from protocol assumptions.

INTRODUCTION

Accelerated repopulation of tumour clonogen during radiotherapy is recognized as an important determinant of tumour control probability. In the late 80s, it was postulated that tumour clonogen proliferation accelerates after 3-4 weeks from the begining of radiation treatment at least in the head and neck tumours and that the second part of irradiation could be especially unsafe in regard to the treatment breaks (Withers et al., 1988). Therefore, in some institutions so called *„escalating-dose regimens"* of radiation treatment were implemented, where the daily tumour dose was progressively escalated during the course of treatment (Harari et al. 1992, Kajanti et al. 1997, Schwade et al. 1992, Maciejewski et al. 1992).

The rationale for this approach proposed in Gliwice in 1988 was to counterbalance tumour repopulation kinetics illustrated by the dog-leg curve of the dose-time relationship. Consequently, a new fractionation schedule was designed: the treatment was divided into two parts of irradiation, separated by a rest period. The first part - hyperfractionation two times daily of 1,6 Gy up to 32 Gy was followed after 7 days of a treatment gap by the second part, delivered by an escalated fraction dose, starting from 1,5 Gy to 2,0 Gy also twice daily.

In this approach the overall treatment time was reduced by about 1,5 - 2 weeks compared with standard fractionation of 2 Gy per day, five times per week.

The aim of this study was to estimate the effectiveness of such a scheme in view of the long-term tumour control and radiation toxicity.

MATERIAL AND METHODS

Between 1988 and 1992, at the Centre Oncology Maria Sklodowska-Curie Memorial Institute in Gliwice, 48 patients with squamous cell cancer of the head and neck were treated with escalated hyperfractionation regimen of radiotherapy.

The study included 44 men and 4 women (mean age - 55 years, range 41-75) with good performance status (ZUBROD 0-1). Their red blood cells counts and haemoglobin levels were within the normal range.
Thirty four patients (71%) had oral cavity cancer, mainly in T2 and T3 stage. In 11 patients (23%)

the tumour was located in the oropharynx, and in three patients (6%) in the larynx. Only 8% of patients had metastases to the single ipsilateral neck node (tab. 1).

	Oral cavity	Oropharynx	Larynx
T-stage	34	11	3
T1	4	-	-
T2	18	6	3
T3	10	1	-
T4	2	-	-
Tx	-	4	-
N1	2	2	-

Table 1. Location and the TN stage

All patients were treated by radiotherapy alone (only one received single course of chemotherapy before irradiation).
Borders of irradiated fields were painted directly on the skin of the head and neck and a customized system was used for the immobilization of patients' head during irradiation.
The treatment plan consisted of two courses of irradiation. The planned total dose depended on the tumour stage, and ranged from 66 to 74Gy. The fraction dose of 1.6 Gy in the first part of the treatment was given by BiD regimen with a 6 h interval, 5 days a week up to the dose of 32Gy. Assuming that the dose intensity of 2,29 Gy/day during the first two weeks of treatment would produce a severe acute mucosal effect, one week of a planned rest period was introduced before dose escalation in the second part of irradiation.

After the planned gap the dose per fraction, also given BiD, was escalated every two days by 0.1Gy, starting from 1.5Gy to 2Gy (fig. 1).

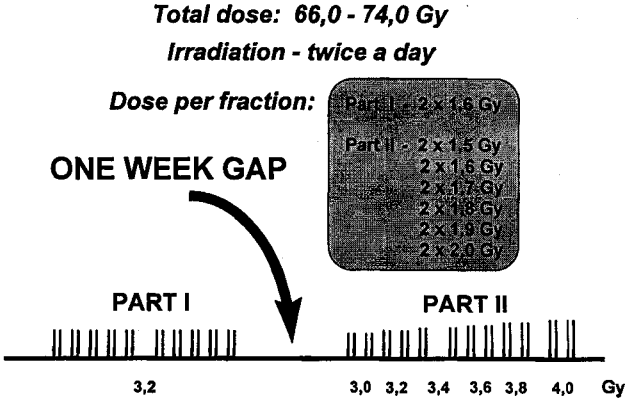

Fig. 1 Scheme of fractionation

All patients were treated with a cobalt unit using a technique of two opposed parallel fields. After reducting the treatment volume (exclusion of the spinal cord) electron irradiation to the posterior cervical nodes was supplemented. Off-cord reduction fields were introduced after the dose in the range between 38 and 44,4 Gy.

The grade of severity of the acute mucosal reaction during the treatment was scored according to the multipunctual European system proposed by Dische et al. (1988, 1989). This system places more emphasis on functional radiation effects, such as dysphagia and odynophagia than on morphological changes (like the EORTC/RTOG system). The former symptoms are highly subjective – varying from patient to patient (e.g. mucositis) in spite of the same score according to the EORTC/RTOG score. The details of the Dische system were described elsewhere (Dische 1988, 1989, Maciejewski 1991).

RESULTS

The average total dose was 68,6 Gy, and it ranged from 62,2 to 74 Gy.
The radiation treatment was completed in 46 patients (96%). Two patients did not complete the treatment because of severe acute mucosal reaction. Intolerance of acute reaction was the reason of the planned gap prolongation in 80% of patients – the mean gap-time being 13 days and ranging from 7 to 25 days. This extended the range of the overall treatment time (OTT) from 33 to 53 days (median: 39 days).

Only two patients did not require supportive treatment with corticosteroids, antibiotics, analgetics and parenteral supplement of liquids.

Complete tumour response (CR) scored directly after completing the irradiation was observed in 75% of patients. Regression rates depending on the tumour site and stage are presented in table 2.

Location of tumour	No	%
oral cavity	24 / 34	71
oropharynx	9 / 11	82
larynx	3 / 3	100
Tumour stage		
T1	4	100
T2	23 / 27	85
T3	5 / 11	45
T4	0 / 2	0
Tx	4 / 4	100

Table 2. Complete tumour regression - location and T-stage

The five-year disease free survival for the whole group of patients was 48% (Fig. 2) and the 5-year local tumour control rate was 54% (Fig 3).

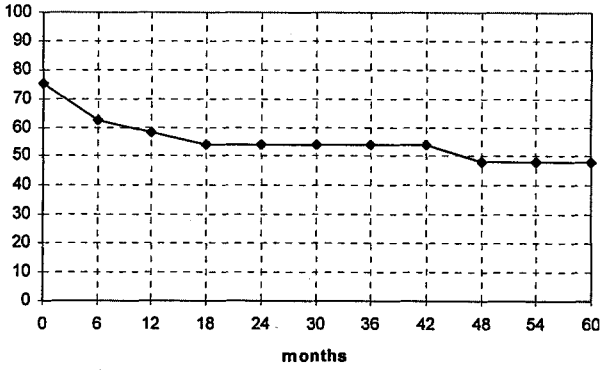

Fig 2. 5-year disease free survival

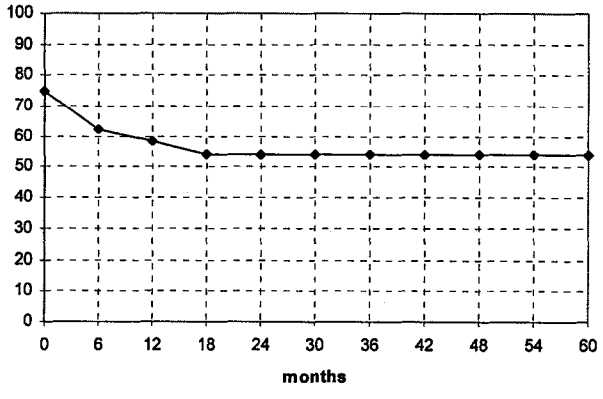

Fig 3. 5-year local tumour control

Local tumour control for T1 tumours was slightly lower than that for T2 tumours: by only 50% and 55% respectively, whereas for Tx it was even 100%. However, the number of patients with T1 and Tx tumours was only 8 (T1-4, Tx-4), therefore the results for T1, T2 and Tx tumours are presented further on one curve.

The five-year local tumour control for T3 tumours was 45% (Fig. 4). No patient with T4 tumour lived longer than 6 months

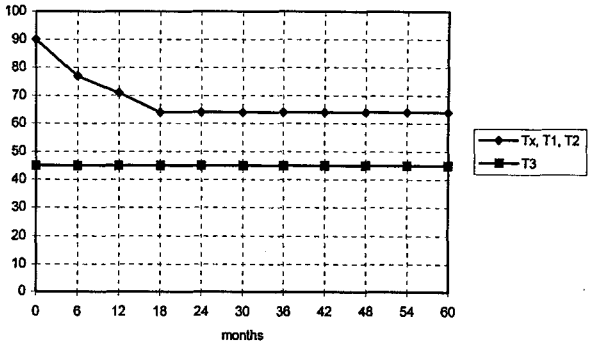

Fig. 4. 5-year local tumour control - T-stage

For the oral cavity cancers (the largest group of cases), the local tumour control rate was equal to disease free survival and ranged from 50% for T1, 44% for T2 to 40% for T3 tumours. (Fig. 5)

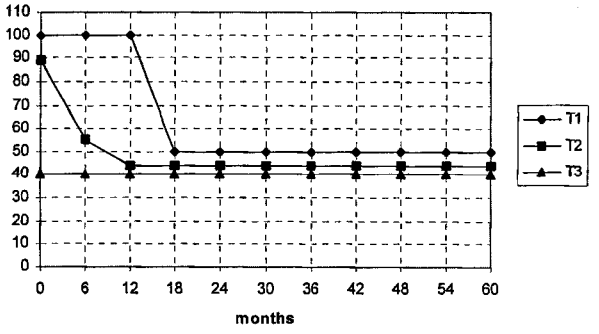

Fig. 5. 5-year local tumour control and disease free survival for oral cavity tumours - T-stage.

An interesting observation is that among 36 pts with CR (75%), 8 (22%) patients experienced local recurrence early after the end of the treatment, that is up to 15 months. There were no local recurrences observed during the follow-up exceeding this period (Fig. 3).

All the patients developed confluent mucositis during the radiation course, which was more intensive than that usually observed during conventional fractionation.

During the first part of irradiation the mucosal reaction was elevated up to the level of confluent mucositis covering more than 50% of the irradiated mucosa.

Tolerance of the second, escalated part of treatment was better than the first one, mainly because of the partial healing of mucous membrane during the gap period (Fig. 6). This acute mucosal toxicity was previously described in detail by Maciejewski et al (1991, 1992).

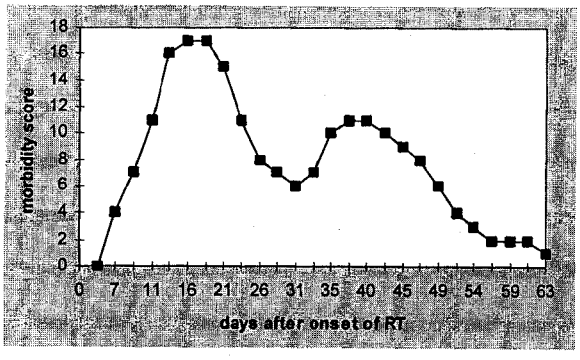

Fig. 6. Mean reactions during escalated hyperfractionation.

Severe (grade IV) late reactions were observed in two patients as necroses of the mandibula. Both patients had cancer of the oral cavity and received the total dose higher than 70Gy. Seven month after completing irradiation one of them had teeth extraction.

No other serious complications were observed.

DISCUSSION

Two main justifications for the introduction of escalated hyperfractionation into the radiotherapy clinical practice was proposed:
- escalation of the daily dose during radiotherapy should counterbalance tumour repopulation as treatment progresses, increasing total tumour cell kill effect and in consequence, giving better results of irradiation,
- less intensive therapy at the beginning of irradiation and a rest period will stimulate rapid proliferation of normal mucosal stem cells, and the patients will probably tolerate better the more intensive irradiation as it progresses.

Four reports concerning escalated hyperfractionation radiotherapy for the head and neck cancer have been published so far (Harari et al. 1992, Kajanti et al. 1997, Maciejewski et al. 1992, Schwade et al. 1992). All of them are brief, preliminary reports and comprise small groups of patients only. Complete tumour regression after completing irradiation ranged from 83 to 93%, which was interpreted as an optimistic prognostic factor. Severe acute reactions during the treatment course were defined as „tolerable", but they were always more severe than those observed during conventional fractionation.

In 1997 Kajanti at al. presented more long-term (3-year) results of irradiation of 29 patients with head and neck cancers in stage III-IV. Complete tumour response at 3 months after radiotherapy was 93%, but the local tumour control dropped after 3 years to 60%. All the patients developed acute mucosal reactions which were completely healed. In 52% of patients hospitalization was needed mainly because of nutritional support, but finally, no serious late complications were observed.

No other long-term reports on escalated fractionation have been published as yet, therefore our results should be compared only with a Finnish study. In this study, authors observed a similar tumour control rates, i.e. 60% (Kajanti et al., 1997) versus 54% in our study. However, our results were concerned mainly with the patients in stage II, whereas in the Finnish study more advanced tumours (stage III and IV) were registered. That is why they had to be given higher total doses of 74 Gy in comparision with 69 Gy in Gliwice. Also in the Finnish study, two-thirds of the patients received the prescribed dose within the planned OTT. In our study, only 20% of cases completed the treatment according to the planned gap duration.

We can state that our study did not show any benefit from the escalated hyperfractionation regime, and the results are comparable with those of a similar historical group treated by

conventional fractionation at our department (Maciejewski et al, 1989). This is especially surprising as regards the expected high probability of tumour cure estimated for those schedules (Fowler et al, 1992).

In our opinion, the observed lack of treatment benefit can a be result of the following factors:

1) treatment rest period

Before begining the study it was assumed that the duration of the planned gap should be only one week. Because of severe confluent mucositis that appeared during the week of OTT (it was earlier and much more severe than that usually observed in standard irradiation), the planned gap had to be extended almost twice. Assuming that the tumour clonogen repopulaion „kicks-on" from the beginning of the third week of OTT (Fowler, 1992), it may be that during the long treatment gap period the lethal effect of the first part of irradiation could have been markedly lost by tumour tumour regeneration.

Kajanti et al. also observed the detrimental effect of treatment time prolongation in their escalated study. None of 10 patients who had longer OTT was cured in comparision with only two out of the 19 patients who received the prescribed dose within the planned time.

Also Wang et al. in their work based on the clinical experience with MGH BID program (hyperfractionated, accelerated schedule somewhat similar to escalated one), point out the deletorious effect of prolonged treatment course as a result of tumour clonogen repopulation which occured during the gap period (Wang et al., 1996).

The importance of treatment gaps for radiotherapy outcome was also investigated by Skladowski et al. (1994). They observed that gaps prior to Day-19, and after Day-29 of OTT during the irradiation of the supraglottic cancer were associated with a lower tumour control probability than the gaps in the middle period of treatment (i.e. between Day-20 and Day-28 of OTT).

The radiobiological explanation of this „gap-position" phenomenon remains unknown, however several possible effects could play a role and result in tumour regeneration (Skladowski, 1996).

The „gap-position" phenomenon has recently been confirmed for all head and neck squamous cell cancers (Skladowski et al., 1998) in a retrospective data set of 2612 patients, and in a view of that, our lower than expected, results could also find some explanation.

The rest period in the escalated regime always began on Day-13 of the OTT, thus within the most „unsafe" time for treatment interruption (Skladowski, 1994, 1998).

2) hazard of geographical miss during the second part of treatment

In the present study, patients were irradiated without stabilization by aquaplast masks, and borders of the irradiated portals were marked directly on the skin. In some patients during the rest period, border lines became effaced and the portals had to be resimulated at the begining of the second (escalated) part of treatment. It was noticed that in those patients radiation fields were reduced on average by 10% of the total area in comparison with the area of the initial fields. The shrinkage of the tumour observed after the first part of the irradiation and rest period may have led the physicians to unintentionally decrease the treatment volume in the second part of the irradiation. Thus, it seems that the incorrect delineation of the primary tumour could an important role in the influence of treatment outcome of escalated irradiation.

Finally, due to the several factors described above we are led to the conclusion that some inconsistencies in the radiation treatment do not enable us to determine objectivly clinical effectiveness of the escalated fractionation schedule.

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