ACUTE AND CONSEQUENTIAL MUCOSAL RADIATION REACTIONS IN PATIENTS WITH HEAD AND NECK CANCER TREATED BY CONTINUOUS ACCELERATED IRRADIATION (CAIR).

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SUMMARY

Acute mucosal and late radiation responses on continuous accelerated irradiation (CAIR) were evaluated and compared with a conventional treatment (control arm) in 85 patients with head and neck cancer. Confluent mucositis was significantly more severe and maximum score lasting longer in CAIR than in control arm. In the CAIR group 5 (22%) late effects (osteo- and soft tissue necrosis) occured early during 2-4 month of follow-up compare to 5% (1 patient) in control group. There was significant correlation between severity of acute reactions and these late effects in CAIR arm, suggesting that they were consequential. The risk of consequential effects could be predicted by proposed time-area units system of integral acute mucosal reaction.

INTRODUCTION

Over the last 15 years the efficacy of many different accelerated, hyperfractionated, or combined fractionation schedules have been tested in pilot and randomized clinical studies (Ang et al., 1990; Kaanders et al., 1992; Lamb et al., 1990; Nguyen et al., 1985; Olmi et al., 1990; Peracchia and Salti, 1981; Saunders et al., 1991; Svoboda, 1984; Wang, 1988). In general, the use of altered fractionation is associated with more severe acute reactions because radiation doses accumulated in time are usually higher than in conventional treatment schedules. Moreover, some treatment schedules have carried a certain risk of severe radiation effects which could be a consequence of uncomplete healing of acute reaction rather than typical late radiation toxicity (Nguyen et al., 1985; Peracchia and Salti, 1981; Svoboda, 1984).

In 1994, at Centre of Oncology Maria Sklodowska-Curie Institute in Gliwice, the randomized clinical trial on Continuous Accelerated Irradiation (CAIR) of head and neck cancer has begun. We used single daily fractions for 7 days a week (including Saturday and Sunday) using constant 24 hour interfraction intervals. This schedule is compared with conventional 5 days per week treatment. During the first year of follow-up unexpectedly high rate of early radiation necrosis occurred in CAIR arm, what was reported immediately (Maciejewski et al., 1996). The aim of this paper is to evaluate the risk of so-called consequential late effects and their relationships with acute mucosal reactions, patients, tumour and treatment parameters.

MATERIAL AND METHOD

Patients

Eighty five patients were enrolled in a randomized clinical trial between January 1, 1994 and March 31, 1996. Only patients with histologically proven squamous cell cancer of the oral cavity, oropharynx, supraglottic larynx and hypopharynx in stage $T_{2-4}N_{0-1}M_0$ were eligible for the trial. Additional criteria for inclusion were: age less or equal 70 years, patient performance status, ZUBROD 0-1, haemoglobin level within the normal range prior to treatment. Patient and treatment characteristics show the uniform distribution of biological, clinical and dose-time parameters in both arms of the trial. (Tab.I)

Table I: Patient characteristics by treatment arm.

Parameter	ARM A - „CAIR"	ARM B - CONTROL
Number of patients	44	41
Median age (years)	55	55
Performance status:		
ZUBROD 0	31	30
ZUBROD 1	13	11
Tumour localization:		
oral cavity	9	10
oropharynx	15	12
hypopharynx	2	3
supraglottic larynx	18	16
Clinical T status:		
T2	7	7
T3	22	20
T4	15	14
Clinical N status:		
N0	34	29
N1	10	12
Median Hb level (g/dl)	14.0	14.3

Fractionation schedules

In arm A (CAIR) a total dose of 66-68 Gy for T_2 and 70-72 for T_3 and T_4 tumours was given in single daily fractions, at 24 hour intervals, 7 days per week including Saturday and Sunday. Overall treatment time ranged from 33 to 40 days (Tab. II). Two opposed "large" fields were used from Monday to Friday, and during Saturday and Sunday small fields (within the large one) were used, the size of which was limited to the primary tumour only.

In arm B, the fractionation schedule differed only by overall treatment time, which ranged from 45 to 55 days because of 5-day-a-week fractionation (Tab II). Shrinking fields were used in the last week of treatment. Dose distribution was optimised by computer treatment planning, and in agreement with the ICRU report 29 (1988) the target absorbed doses were specified at the midplane point.

The standard dose per fraction in the trial was 2.0 Gy. During the first year of the study a 22% of early necrosis was observed in the CAIR group (Maciejewski et al., 1996). For this reason in the middle of 1995 we decreased the daily dose by 10% and the standard fraction dose of the trial became 1.8 Gy.

Quantifying acute reactions

All patients were examined independently by the same 4 radiation oncologists (2 of them have been qualified specialists in both radiotherapy and laryngology) and both tumour response and acute mucosal reaction were assessed, at least once a week during the treatment. During the first 2 months of follow-up tumour and normal tissue response was scored every 2 weeks, and subsequently every one month during the first year of follow-up. Mucosal reaction score was recorded using the modified Dische system (Dische et al., 1989, 1994) because it places emphasis on both morphological and functional radiation effects, especially dysphagia and odynophagia and subjective reaction of individual patient to the given treatment. Mean values of scores of all items given by independent 4 observers were added up and the sum was taken as a measure of the objective and subjective acute radiation effect. Thus mucosal reaction score could be qualified within the range of 0 - 30 points.

Supportive treatment

In order to prevent breaks during the treatment patients with acute mucosal reaction rapidly progressing in severity (Dische system score ≥10) received anti-inflammatory drugs starting from local nonsteroids and antiseptic liquids. When severity of mucositis exceeds score 15, systemic corticosteroids and antibiotics, and parenteral supplement of nutrition usually were needed. No any patients required the tube feeding during the treatment. Supportive treatment was given to 40 patients (91%) in CAIR and 22 patients (54%) in control arm, and it usually started at the end of second or third week of radiotherapy, and was discontinued when severe reactions began to heal and patient tolerance to treatment improved.

RESULTS

Acute mucositis

Figure 1 shows the time course of the mucosal reactions according to the Dische scale, plotting the mean scores and their 95% CI. The earliest mucosal reactions, mainly mild redness, were observed one week after the start of treatment. Severity of acute mucositis increased rapidly in both arms of the study between the day 7th and 21st, to reach confluent mucositis covering the entire field in the CAIR group. In the control arm the first spots of mucositis were observed after 3 weeks of irradiation. The most severe mucosal reactions (score > 15) lasting at least 2 weeks were observed in 68% of patients in CAIR arm and only in 28% in control arm (Fig. 1).

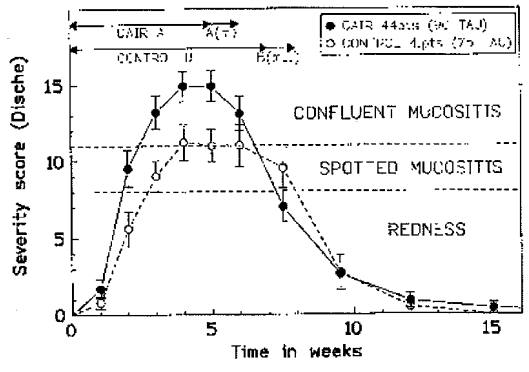

Fig. 1. Acute mucosal reaction course in CAIR and control arms. Points and ranges represent the mean values of mucosal reaction intensity with 95% confidence interval. A - CAIR by 2.0 Gy per fraction, A(m) - modyfied CAIR by 1.8 Gy per fraction, B - conventional irradiation by 2.0 Gy per fraction, B(m) - modyfied conventional irradiation by 1.8 Gy per fraction.

Although the majority of patients in CAIR suffered from severe acute mucosal reactions, all of them except one (98%) were able to tolerate the whole prescribed treatment without breaks. Another one patient in CAIR arm has not completed the treatment due to intercurrent rectal bleeding with no relation to radiation. In control arm also in one patient the treatment has not been completed because of mucositis intolerance.

Figure 1 shows that the whole course of acute mucosal reaction in CAIR irradiation is much more severe than in conventional one. In present study time-area units (field size of area under the curve) were calculated as a measure of integral value of acute mucositis reaction in function of time. This parameter strongly correlates with the intensity of acute mucosal reaction during the whole treatment and postreatment course, especially with the peak/plato phase and healing phase. The integral acute mucosal reaction in CAIR group was about 20% more severe than for patients in control arm (90 time-area units versus 75 respectively, Fig. 1). The change in fraction dose from 2.0 to 1.8 Gy per day, introduced since 1995, gives in CAIR arm the decrease of time-area units of about 15% (95 vs. 83,5) in spite of average increasing the overall treatment time by 4 days. In control arm the same change in fraction dose has not given almost any decrease in time-area units (77 vs. 75 respectively); the overall treatment time was also expand in this schedule by 4 days.

"Late" effects

All patients in control arm (B) have had a complete healing of acute mucosal reaction. In CAIR arm (A) healing of confluent mucositis was prolonged in 12 patients (29%); 7 of them needed for complete healing an extra 2-3 weeks but remaining 5 patients developed during the 2nd to 4th month from the begining of treatment the early mucosal necrosis. It progress rapidly in 3 patients to mandibular necrosis and in following 2 to soft tissue necrosis. There was no early mucosal necrosis in control arm of the study (Tab. III). Persisted massive oedema of the larynx (grade III) was observed during the 3rd month after the begining of treatment in 1 patient (2%) in CAIR and in anyone in the arm B (Tab. III). Clinically, these 6 "late" sequelaes appeared to be a consequential effects (CLE).

Table II. Fractionation trial design

Fraction dose (Gy)	No. of fractions	Total dose (Gy)	Fractions interval	Overall duration of RT	Week 1	2	3	4	5	6	7	8
ARM A - *Continuous Accelerated Ir-Radiation (CAIR)*												
1994												
2,0	33-36	66-72	24h	33-36 days	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII							
1995												
1,8	37-40	66,6-72	24h	37-40 days	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII							
ARM B - *Conventional Irradiation (Control)*												
1994												
2,0	33-36	66-72	24h	45-50 days	IIIII	IIIII	IIIII	IIIII	IIIII	IIIII	IIIII	I
1995												
1,8	37-40	66,6-72	24h	51-54 days	IIIII	IIIII	IIIII	IIIII	IIIII	IIIII	IIIII	IIIII

Table III. Late radiation toxicity

EORTC/RTOG	ARM A - „CAIR"		ARM B - CONTROL	
	fr. dose = 2,0 Gy 1994	fr. dose = 1,8 Gy 1995	fr. dose = 2,0 Gy 1994	fr. dose = 1,8 Gy 1995
	23 pts	19 pts	21 pts	19 pts
0	1 (4%)	6 (32%)	6 (28%)	9 (47%)
1	11 (48%)	10 (53%)	5 (24%)	6 (32%)
2	5 (22%)	2 (10%)	7 (33%)	4 (21%)
3	1 (4%)	1 (5%)*	3 (15%)	0
4	5 (22%)*	0	0	0

*** in all pts late-type reaction appeared consequently within 2-4 months after the end of RT**

In our first paper concerning this trial (Maciejewski et al., 1996), we reported on 7 patients with consequential necrosis, but in 2 of them the persistent and ulcerative primary tumour was misdiagnosed as a necrosis in spite of the negative biopsies done during the first months of follow-up.

Five early necrosis occurred only within the group of 23 patients (22%) irradiated in the year 1994 when standard dose of the trial 2.0 Gy per fraction was used and this was the reason to diminish the fraction dose to 1.8 Gy in the both arms. A multiple biopsies were taken rom the necrotic area and histologic examination revealed no evidence of tumour cells in all 5 cases and median time of follow-up is 25 months. Two patients were admitted to reconstructive surgery: others 3 refused surgical intervention, and received symptomatic treatment only. There was no increase in the severity of this effect during follow-up, and it was tolerated by patients supported by antibiotics and anti-inflammatory treatment. The spontaneous complete healing of necrosis occurred in 2 patients after 10 and 18 months of follow-up (Tab. IV).

Table IV. Consequential late effects

TRIAL ARM	CHARACTERISTICS	APPEARANCE	TREATMENT	SURVIVAL
A - CAIR d. fr. = 1,8 Gy	Massive edema of larynx EORTC/RTOG - 3	3rd month	antibiotics steroids maintenance of tracheostoma	24 months alive
A - CAIR d. fr. = 2,0 Gy	Necrosis of right tonsillar fossa	4th month	oxygen antibiotics	20 months alive
A - CAIR d. fr. = 2,0 Gy	Necrosis of right pharyngeal wall	3rd month	antibiotics complete healing after 10 mths	27 months alive
A - CAIR d.fr. = 2,0 Gy	Necrosis of right retromolar area	3rd month	oxygen surgery	21 months alive
A - CAIR d. fr. = 2,0 Gy	Necrosis of right retromolar area	3rd month	oxygen antibiotics complete healing after 18 mths	24 months alive
A - CAIR d. fr. = 2,0 Gy	Necrosis of mouth floor	2nd month	surgery	25 months alive

Table V. Clinical and treatment factors associated with consequential „late" effects

FACTOR	CLE - 6 pts	NO CLE - 36 pts	probability
Mucosal weakness by tumor ulceration	**5/6 (83%)**	**11/36 (31%)**	**$p < 0.05$**
Tumour fixation	**5/6 (83%)**	**12/36 (33%)**	**ns**
T_4	**4/6 (67%)**	**10/36 (28%)**	**ns**
Performance status deterioration during RT	**6/6**	**16/36 (44%)**	**ns**
Hemoglobin loss during RT (g/dl ± 95%CI)	**-1,4 ± 0,1**	**-0,8 ± 0,4**	**$p = 0.05$**
Primary radiation field (cm^2)	**130 ± 15**	**119 ± 6**	**ns**
Off-spinal cord radiation field (cm^2)	**90 ± 26**	**76 ± 7**	**ns**
Weekend-boost radiation field (cm^2)	**35 ± 5**	**34 ± 3**	**ns**
Maximal total dose (Gy ± 95%CI)	**76,4 ± 1,8**	**74,5 ± 1,0**	**ns**
Maximal dose per fraction (Gy ± 95%CI)	**2,12 ± 0,04**	**1,98 ± 0,1**	**$p = 0.05$**
Maximal biological dose accumulated per week	(α/β=2Gy): **15,3 Gy** (α/β=5Gy): **15,1 Gy**	(α/β=2Gy): **13,8 Gy** (α/β=5Gy): **13,8 Gy**	**$p < 0.05$** **$p = 0.05$**
Acute mucosal reaction intensity (relative units ± 95%CI)	**1,35 ± 0,18**	**1 ± 0,1**	**$p < 0.01$**

For several clinical and physical factors the association with early mucosal necrosis was evaluated (Tab. V). All 5 patients received a total dose of 72 Gy, and necrosis occurred only within the tumour bed which has been irradiated continuously, every 24 hour, by Saturday-Sunday boost fields treatment. In all patients with necrosis the performance status and haemoglobin level deteriorated significantly during the treatment course. In 4 of 5 patients the primary tumour was ulcerated and fixed with deep infiltration to the pharyngeal and oral cavity wall; as well, all these patients had poor dentition prior to treatment.

Five of six patients in subgroup with CLE had the highest score (>15) for acute confluent mucositis lasting longer than 3 weeks during treatment (Fig. 2, Tab. V). Severe and persisted acute mucosal reactions were significantly predictive for CLE; for patients who developed necrosis the mean overall severity of acute radiation mucositis measured by the time-area units was relatively 35% higher than for other patients in CAIR arm ($p < 0.01$).

fig. 2

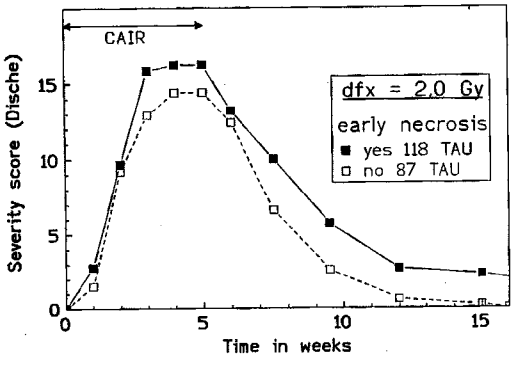

Fig. 2. Acute mucosal reaction course in CAIR arm. Comparison between the subgroups of patients with CLE and with no CLE.

Analysis of individual isodose distribution showed that mucosal necrosis developed within the area where total and fraction dose were planned at their maximum. The estimated values of 76,4 Gy of total dose and 2,12 Gy of dose per fraction estimated for the area of necrosis were clearly higher than for other patients in CAIR arm. Assuming that for

mucosal necrosis α/β ratio is 2 or 5 Gy (Kaanders and Ang, 1994) and using the linear-quadratic formula (Withers et al., 1989) the biological accumulated dose per week within the necrosis bed could be as high as 15,3 Gy or 15,1 Gy respectively instead of planned 14 Gy per week.

We also note that there is an association between the occurrence of CLE and other factors, in particular, "late" effects tended to occur in patients treated with larger fields and experienced greater weight loss. But for none of these factors was the association as strong as between some of the acute response characteristics and the CLE.

The estimated risk of consequential necrosis in relation to the integral acute mucosal reaction expressing by the values of time-area units is shown in Figure 3. The 50% risk of early mucosal necrosis is associated with the 155 time-area units, i.e. with the course of acute mucositis about 2-times more severe than that accompanied with conventional irradiation 2 Gy per day, 5 days in week to 70 Gy (75 time-area units).

fig. 3

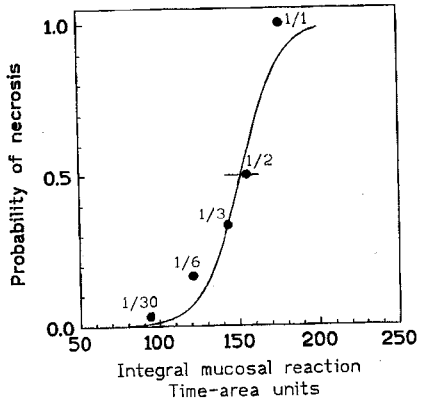

Fig. 3. Sigmoid curve of the risk of consequential „late" mucosal necrosis as a function of overall severity of mucositis in CAIR arm.

DISCUSSION

There is now a substantial number of studies on radiotherapy for head and neck cancer using altered fractionation schedules and nearly all document an increased incidence or severity of acute mucosal reactions. Thus, when one considers alternative fractionation strategies, acute mucosal reactions become most significant dose-limiting of radiation tolerance because mucosa is very sensitive to **dose accumulated in time** (Kaanders and Ang, 1994, Skladowski et al., 1996). In conventional radiotherapy, it has been empirically shown that the majority of patients can comfortably complete the treatment without excessive acute toxicity when the accumulated dose per week (ADW) is 9-10 Gy. For example, Fletcher (1980) reported that after an ADW of 10 Gy, 75% of patients showed signs of healing during the last week of treatment. This proportion dramatically decreased to only 15% after moderate increase in the ADW to 12 Gy. Accelerated and hyperfractionated schedules are the strategies designed to improve tumour control rate with no or little increase of late sequelae but in aspect of early toxicity these strategies involve a higher ADW than conventional treatment and, in consequence, the increased severity of acute mucosal reactions are reported (Ang et al., 1990; Horiot et al., 1992; Kaanders et al., 1992; Lamb et al., 1990; Nguyen et al., 1985; Olmi et al., 1990; Peracchia and Salti, 1981; Saunders et al., 1991; Svoboda, 1984; Van der Schueren et al., 1990; Wang, 1988).

Early side effects of the mucous membrane in radiation therapy of the head and neck cancers are generally the result of proliferating cell death in its rapidly renewing stem-cell and transit-cell compartments. Clinical observations and results of laboratory studies suggest that the intensity of acute epithelial reactions, like other H-type tissues, reflects the balance between the rate of cell killing by radiation and the rate of surviving stem cells regeneration. Once a critical level of survival cells has been attained, a certain type of clinical damage will develop at a rate determined only by the cellular kinetics of the mucosa. When a peak of mucositis intensity is reached, further stem cell killing can not produce an increase in intensity of acute reactions, but could be manifest as prolonged time to heal. When acute mucositis is extremely severe, late effects, as radionecrosis, may develop soon after the complete of treatment as a direct consequence of acute injury; these are called *consequential late injuries*. Consequential late injury evolves when complete epithelial denudation occurs with no surviving cells within the irradiated volume such that healing, if it occurs at all, must take place entirely by repopulation of cells from the periphery of the radiation field (Kaanders and Ang, 1994).

In our study the ADW of 14 Gy and later on 12,6 Gy in CAIR was not so high as in some studies of accelerated repopulation (Nguyen et al., 1985; Olmi et al., 1990; Peracchia and Salti, 1981; Saunders et al., 1991; Svoboda, 1984), but was constant during the whole treatment period (5-6 weeks). Confluent mucositis was reached sooner, persisted longer, and complete

healing was delayed compare to the control arm where ADW was 10 Gy or 9 Gy (Fig. 1). Although all CAIR patients, except one, tolerated well the acute radiation toxicity, quite unexpectedly, mucosal radionecrosis occurred in 5 patients (22%) during 7-12 weeks after completing the treatment. This suggests that ADW is probably not the only parameter determining acute mucosal reactions, but also the rate at which dose is accumulated over the whole course of the treatment may have an important impact on overall severity and healing-time of acute reaction.

Early development of mucosal necrosis after the end treatment in 5 CAIR patients has proven that it is a consequence of deep mucosal radiation injury rather than a typical late radiation reaction. The acute effect characteristics which are most strongly associated in our study with the consequential late effects are those which involve a high average score persisted for a long time (Fig.2). Furthermore, in all 5 patients with consequential necrosis the healing of mucosal reaction was delayed and uncompleted. This suggests that the maximum acute effect, its duration at a high level and the delayed healing are the important combination of factors, rather than just one of them. Intensive, severe and persisted acute mucosal reactions were highly predictive for consequential effects (Tab. V). Prophylactic parenteral nutrition, antibiotics and corticosteroids administered to improve tolerance and healing of acute mucositis probably did not prevent consequential late effects.

The value of ADW is probably the best parameter for prediction of the intensity of radiation mucositis. However, to predict the risk of consequential effects for a given treatment schedule, an additional parameter - time-area units system - has been proposed. This way to estimate the overall severity of acute mucositis gives, in our opinion, the useful information on risk of consequential mucosal necrosis for individual patients and fractionation. Careful measurement of integral mucosal reaction in time-area units on the base of multifactoral scoring system could help to predict the risk of consequential effect even when altered, irregular fractionation be contributed (Skladowski et al., 1996). The system proposed by Dische (1989) is a spread of EORTC/RTOG glossary and places emphasis on functional radiation effects and morphological changes. The determination of proper functional score, like grade of odynophagia, is highly subjective and needs well-experienced interviewer. But the expanded range of score (up to 30 points) is allowed to monitor the differences in the individual intensity of confluent mucositis, specially in accelerated intensive treatment, and, perhaps, to alarm the risk of consequential injuries.

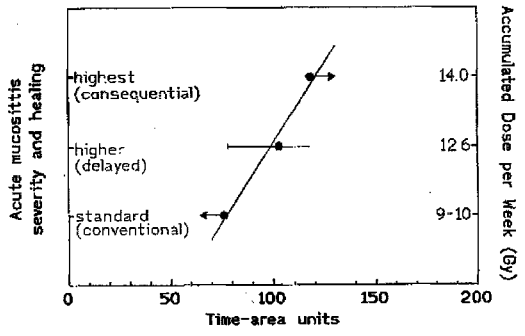

Fig. 4. Time-area units as a prognostic factor of severity and healing of acute mucosal reaction.

As is presented in Figure 4, CAIR irradiation with 14 Gy of ADW corresponding in the overall severity of mucositis approaching or exceeding 120 time-area units is correlated with high risk (~10-20%) of consequential mucosal necrosis. The problem in mucosal healing should be expected when the overall severity of mucositis is in amount of 80-120 time area units (ADW - 12.6 Gy). For patients irradiated by the same fraction doses but with weekend breaks (control arm, ADW = 9-10 Gy) the overall severity of mucosal reaction rarely exceeds 80 time area units, the risk of CLE is low (< 1-2%) and mucosal healing for majority of patients is undisturbed (Fig. 4).

There is the question if enhanced overall severity of mucositis is the result of individual radiosensitivity or reflects the inhomogenity of dose distribution within the irradiated target volume (Bentzen and Overgaard, 1996). For all patients with CLE the maximal planned dose was located within the area of further necrosis and usually exceeded the planned dose by about 8%. If we assume that α/β ratio for mucosal CLE is in the range 2-5 Gy (Kaanders and Ang, 1994) then biological ADW in necrosis area could be, as high, as 15.1-15.3 Gy for the whole treatment period of 5 weeks. Van der Schueren et al. (1990) suggest that oral mucosa needs very little time for recovering and under the pressure of radiation induced cell killing in capable of compensating for the effect of about 1.8 Gy/day. Our previous (Maciejewski et al., 1991) and present results support this suggestion, showing that even a short 2-day radiation break during the weekend, and a 2 week prolongation of overall treatment

time, play an important role in physiological response of compensating repopulation of mucosal stem cell. Our 7-day CAIR fractionation of 2 Gy a day during 5 weeks dangerously „shacked" the balance between cell killing and repopulation, although interfraction intervals were always 24 hours. Therefore it should be not surprised that in such extremely strained mechanisms of recovery even a small exceed of accumulated dose could given complete denudation of mucosal stem cells and in the final result - early necrosis.

Kaanders et al. (1992) suggest that besides dose and fractionation such factors as field size, sites treated and general patient condition may also play an important role in development of consequential late effects. In the present series there was the trend to use the larger primary and off-spinal cord radiation fields in patients who developed CLE (Tab. V). The mean size of „weekend-boost" fields was identical in both groups, but the consequential effects always developed in the bed of primary tumour, within a small area of mucosa which was irradiated 7-days a week, and never within a larger field which received 5 fractions per week. Also the physiological condition of the mucosa was weakened by tumour ulceration and mass of deep infiltration in majority of patients to begin with the treatment. The performance status of all patients was good (ZUBROD 0-1) at the begining of treatment, but during radiation therapy deteriorated in all 6 patients with CLE (Tab. V). We observed also during the treatment time more deep decline of haemoglobin in these patients than in others from CAIR arm (p=0.05). These observations suggest that an additional factors related to the patient condition may play the additive role in development of consequential mucosal injuries.

CONCLUSIONS

Regular accumulation of radiation dose in equal or above 14Gy/week produces severe acute mucosal reaction, what in association with poor mucosal condition could provide to defect of mucosal healing. The continuous treatment with 1,8Gy a day gives lower accumulation dose in time and as yet seems to be safe and quite tolerable.

The estimation of integral severity of mucosal radiation reaction by proposed time-area units system should make possible to predict the risk of consequential late effect or delayed mucosal healing for given fractionation schedule in individual patient.

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