RADIOBIOLOGICAL BASIS, INCIDENCE AND KINETICS OF ACUTE MUCOSAL REACTION AFTER DIFFERENT FRACTIONATION SCHEMES

K. SKŁADOWSKI[1], A. ZAJUSZ[2], R. TARNAWSKI[1], B. MACIEJEWSKI[1]

1. Radiotherapy Clinic 2. Teleradiotherapy Dept., M. Skłodowska-Curie Cancer Centre and Institute, 44-100 Gliwice, Poland Wybrzeże Armii Krajowej 15

ABSTRACT

The paper is presented essential practical knowledge about acute mucosal reactions as an effect of radiation therapy in patients with head and neck cancers. The authors have presented their own experience with mucosal reactions in the course of different fractionation schedules. The practical use of Accumulated Dose in Time and Dose-Time Ratio as a parameters of the risk, intensity and overall heaviness of radiation mucositis is proposed.

Key words: acute mucosal reaction, accumulated dose in time, dose-time ratio

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 (Kaanders and Ang, 1994). During conventionally fractionated treatment, the acute mucosal reaction is mostly within acceptable limit. However, new radiotherapy strategies, like hyperfractionation, accelerated fractionation and combination of irradiation and chemotherapy, induce more severe acute toxicity and the mucosal reaction is elevated to the upper limit of tolerance. Therefore, the effective and quantitative monitoring and the knowledge about the prevention and treatment of this side effect are essential for further development of therapy in head and neck cancer.

CLINICAL COURSE OF ACUTE MUCOSITIS

During radiation treatment, mucosal *erythema* develops very early (within 1 week) after the start of irradiation. The basal layer of the epithelium shows degenerative changes, the underlying submucosa becomes edematous with dilatation of capillaries as an effect of accumulation of mucous secretions in the minor salivary glands and inflammatory reaction. At about 2 weeks, the reddened mucous membrane develops small white or yellow patches of fibrin, leukocytes and necrotic epithelium called *mucositis* or *false membrane formation*. In many of patients, the *patchy mucositis* becomes *confluent* by the 3rd week of irradiation and usually persists in that intensity until the end of treatment. Mucosal healing starts after the end of radiation and in majority of patients all signs of mucositis disappear within 5 weeks.

Different anatomical mucosal areas within upper aerodigestive tract do not respond uniformly to radiation. The soft palate, tonsillar folds, buccal mucosa, lateral border of the tongue, pharyngeal walls and epilarynx readily developed mucositis than other sites, such as hard palate, gingivas, dorsum of the tongue and true vocal cords. Mucositis often first appears over the tumour itself, as early as at the end of first treatment week, especially over the exophytic or ulcerative oropharyngeal tumour. This early tumour reaction sharply demarcates the area of tumour involvement and is often called *tumoritis*.

FRACTIONATION SENSITIVITY

Clinical observations give evidences that radiation mucosal reaction is sensitive to changes in time-dose-volume relationships. At fractionation of 2.5 Gy five times weekly confluent mucositis is seen in all patients during the treatment course, whereas the dose administered at 2 Gy per fraction results in patchy mucositis in the majority of them. Prolongation of treatment time by introductions of a gap during the treatment course or fraction dose decrease to 1.6-1.8 Gy reduces mucosal

reactions to only marked redness or small areas of patchy mucositis. Irradiation of several fractions (2-4) per day usually produces severe mucosal reaction at the end of 2nd week of treatment. On the other hand, the objective signs of mucositis healing are not seldom seen during the irradiation, mainly at the last week of treatment.

This clinical evidences and results of laboratory studies (Kaanders and Ang, 1994) shown several importances in practice: (1) the intensity of mucosal reaction clearly depends on accumulation of radiation dose in time; (2) half time of cellular repair of mucosal tissue is around 1 hour, i.e. 4-5 hours are needed for complete repair of sublethal radiation injuries; (3) the α/β ratio for early mucosal reaction (4-5 Gy) is possibly lower than for other acutely responding normal tissues, it may suggest that the fraction size and amount of total dose could have a role in overall reaction heaviness; (4) compensatory mucosal proliferation increases over the course of fractionated irradiation and may counteract even whole fraction dose at the final part of the treatment; (5) the subjective patient complaints due to mucositis are roughly connected with the amount of irradiated volume, i.e. treatment field size; (6) radioresponsiveness (radiosensitivity?) of the mucosa is not uniform for all anatomic sites within upper aerodigestive tract.

KINETICS OF ACUTE MUCOSITIS

All these observations 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 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.

UNIFORM REPORTING OF RADIATION MUCOSITIS

Fletcher divided acute mucositis into three grades: **(1) redness, (2) spotted mucositis and (3) confluent mucositis**. Redness was further subdivided into **mild redness** and „angry red that characterizes increasing reaction" i.e. **severe redness**. This simple grading system, or its minor variations, is still widely used and accepted (EORTC/RTOG scale). However, in clinical practice when the altered aggressive treatment is administered, almost all patients reach highest, fourth, level of mucosal radiation toxicity and further individual differences in reaction intensity disappear.

The system proposed by Dische (Dische, 1994) is a spread of EORTC/RTOG glossary and places more emphasis on functional radiation effects than on 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 (~ 30 points) is allowed to monitor the differences in the individual intensity of confluent mucositis and, perhaps, to alarm the risk of consequential injuries.

ACCUMULATED DOSE IN TIME

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 and 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 **accumulated dose in time** (ADT). Accelerated and hyperfractionated schedules are 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 ADT than conventional treatment (Tab. I).

Analysis of the data sets of accelerated and hyperfractionated radiation treatments shows that, except with hyperfractionation and short single course of accelerated regimens, the ADT is not constant within whole treatment time. High ADT, above 25 Gy/week (4-5 Gy/d), is typical for accelerated treatments when the dose is lowered and condensed into a single course with short overall treatment time (CHART) (Saunders et al, 1991). In concomitant boost schedule (Ang et al, 1990) a high ADT of 16.5

Gy/week is delivered either in begining or final two weeks of treatment and in the remaining 4 weeks ADT is not as high as 9 Gy, or is equally (11 Gy) distributed within the overall treatment time. In double-BID-split course schedule [3] the ADT of 16 Gy is given in the first 2,5 weeks and the final 1,5 week separated by 2 weeks of treatment break (ADT = 0 Gy). As yet, the ADT seems to be the best parameter reflecting the rate of increase and intensity of acute radiation effects (6,7,8).

DOSE-TIME RATIO

It is not easy, or sometimes even impossible, to express the ADT as a single stable value for prediction of the **overall** risk and heaviness of mucosal reaction for a given treatment schedule. For that reason, an additional factor, **Dose-Time Ratio** (DTR) was proposed to introduced to this problem. Dose-Time Ratio is a product of ADT, Total Dose (TD) and number of days when irradiation is given (Radiation Days - RD). Factor of DTR can be written:

$$DTR = \frac{ADT \cdot TD \cdot RD}{1000}$$

and is quantified in Gy^2/day^2. For conventional treatment of 2 Gy per fraction, 5 times a week (ADT = 1,43 Gy/d), up to TD of 70 Gy and 35 radiation days, the DTR is equal 3,5 Gy^2/d^2.

Table I shows the DTR values for most popular fractionation schemes in clinical practice. Dose-time ratio seems to be useful to compare different fractionation schedules in aspect of general risk and heaviness of acute radiation mucosal reaction, provided that interfraction time interval is long enough for full radiation repair (around 6 hours). Also, in our opinion, that parameter is sufficient to predict the risk of consequential late necrosis within the irradiated volume.

GLIWICE EXPERIENCES

Assessment of dose fractionation factors influencing the rate of increment, peak intensity, course and overall heaviness of acute radiation mucosal toxicity during 4 different fractionation schedules in radiotherapy of head and neck cancers is the purpose of the analysis.

In 133 patients with squamous cell carcinoma of oral cavity, oropharynx, hypopharynx and supraglottic larynx the acute mucosal reaction during the course and after irradiation was investigated. All patients were in clinical stages T2-4 N0-1, in performance status Zubrod < 2 and have had no prior therapy. Forty six patients were irradiated in conventional fractionation scheme, 5 times a week with 1,8-2 Gy per fraction up to 66-72 Gy of total dose within 45-50 days and present the control group (**A**) of this study. In continuous fractionation group (**B**), 47 patients were irradiated by 7 days a week (including Saturdays and Sundays) with 1,8-2 Gy fractions up to 66-72 Gy in 33-40 days. The 3rd (**C**) group including 15 patients all fractionation parameters were like in B group with one except that weekend breaks were introduced but second doses were added at Tuesdays and Fridays as a concomitant boost. In last group (**D**), 25 patients were irradiated by BID/split/escalated BID schedule (first 32 Gy, two times daily 1,6 Gy fraction, then 7-12 days of a treatment break and again 34-40 Gy two times per day by escalated fraction dose from 1,6 to 2,0 Gy) up to 66-72 Gy in 5 weeks [Van der Schueren et al, 1990]. Every treatment course has started from Monday. Acute mucosal reaction was assessed in each patient every Monday during the 7-week inpatient observation, then at control follow-up visits, using the scale proposed by Dische et al [6]. Every time when the total score succeeded the 10 points or above the parenteral anti-inflammatory treatment was introduced.

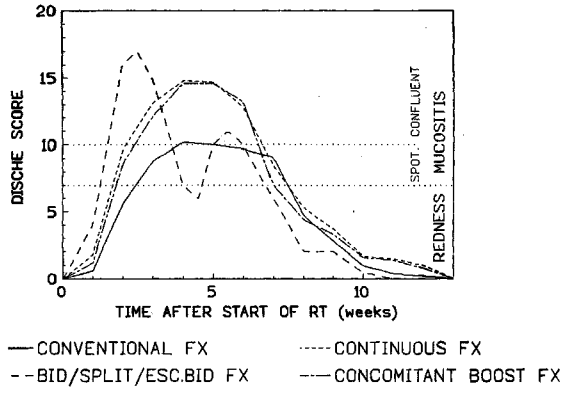
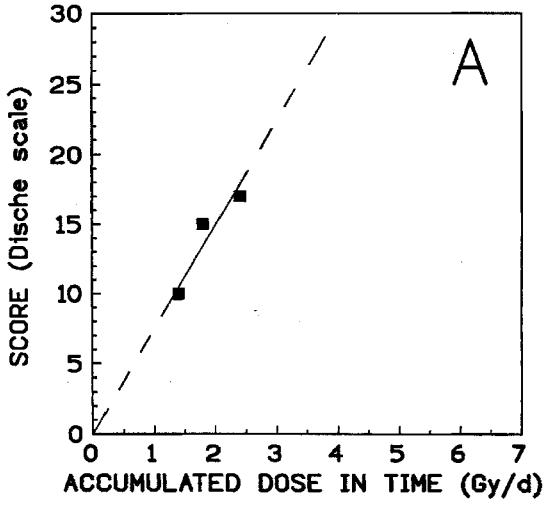


Fig. 1: The comparison of the coures of acute mucosal reaction in 4 different fractionation schedules in Gliwice experiences.

The ADT was different between the analysed groups of patients (1,43 Gy/d in A, 2Gy/d in B and C, and ~ 2,5 Gy/d in D). There were no any differences in mucosal reaction between the groups B and C in spite of weekend treatment breaks (Fig. 1). The increase of confluent mucositis was developed at first 2-4 weeks of treatment and its rate clearly depended

on ADT, as well as, the peak of intensity (Fig. 2A). Also the time when mucositis reached the maximum score was different between the groups: second and half week in D versus 4th week in A-C (Fig. 1). The introduction of treatment gap in D schedule allowed severe confluent mucositis to partial healing before the second part of treatment, but the second wave of intensity was lower than that associated with first part of irradiation in spite of increasing ADT. The overall heaviness of radiation reaction (estimated in this study as an area under the curves) in group B/C and D was ~ 50% and ~ 25% respectively more severe than in control group A and this data were consistent with the comparison of DTRs of groups B/C and D to group A (Fig. 2B).



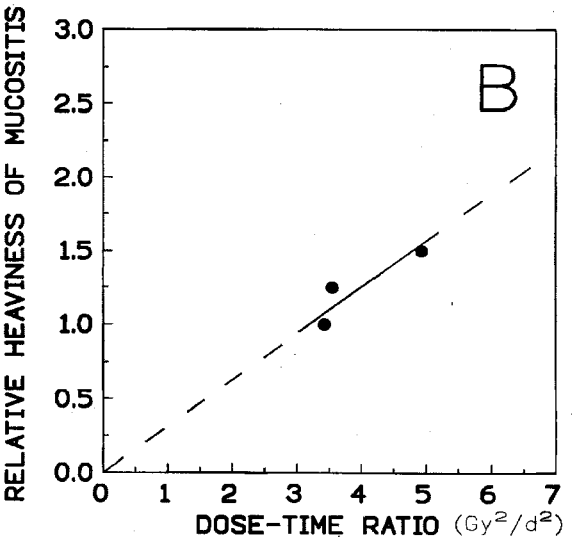


Figure 2A: The relationship between the rate of mucositis intensity estimated in Gliwice study and Accumulated Dose in Time (ATD).
Figure 2B: The relationship between the overall heaviness od acute mucosal reaction estimated in Gliwice experiences and Dose-Time Ratio (DTR).

The rate of healing of acute mucositis showed discrete differences between the analysed groups of patients and was independent on overall treatment time. The process of mucosal healing seems to be associated rather with overall heaviness of mucosal reaction i.e. high values of DTR and risk of consequential necrosis; in group B/C consequential soft tissue or bone necrosis occurred in 5 patients (8%) compare to 1 patient (2%) with necrosis in group A.

Table I. The values of Accumulated Dose in Time (ADT) and Dose-Time Ratio (DTR) for most popular fractionation schedules.

Fractionation Type	Fractionation Parameters	ADT (Gy/day)	DTR (Gy^2/day^2)
Conventional (A)	70Gy/35Fx/50days	1,4	3,43
Hypofractionation*	51Gy/17Fx/ 23days	2,2	1,92
Hypofractionation#	40Gy/10Fx/30days	1,3	0,53
Split-course#	70Gy/28Fx/50days	1,4	2,74
Hyperfractionation [9]	80,5Gy/70Fx/50days	1,6	4,54
CHART [5]	54Gy/36Fx/12days	4,5	2,92
BID/SPLIT/BID [3]	67,2Gy/42Fx/32days	2,1	2,96
Concomitant boost [4]	72Gy/42Fx/40days	1,8	3,89
Gliwice Study			
Continuous (B)	70,2Gy/39Fx/39days	1,8	4,93
Concomitant boost (C)	70,2Gy/39Fx/39days	1,8	4,93
BID/SPLIT/ESC-BID (D)	70Gy/41Fx/ 36days	2,4	3,55

(*) Manchester school, (#) Gliwice experiences

Our study suggests that: (1) the rate of increasing acute mucosal reaction depends on accumulated dose in time; (2) the rate of its healing and risk of consequential late effects seems to be dependent on overall heaviness of mucositis what correlated with high value of DTR in our study; (3) treatment gaps allow the partial healing what diminishes the intensity of mucositis in renewal irradiation; (4) precise scoring and monitoring system of acute mucosal reaction is essential in clinical practice and can help to avoid severe postradiation complications in patients with head and neck cancer.

REFERENCES

1. Ang K.K., Peters L.J., Weber R.S. et al: Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int. J. Radiat. Oncol. Biol. Phys. 19, 1990: 1339-45;
2. Dische S.: The uniform reporting of treatment-related morbidity. Seminars Radiat. Oncol. 4, 2, 1994: 112-118;
3. Horiot J.C., Le Fur R., N' Guyen T. et al: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy
4. Kaanders J.H., Ang K.K.: Early reactions as dose-limiting factors in radiotherapy. Seminars Radiat. Oncol. 4, 2, 1994: 55-67;
5. Peters L.J., Brock W.A., Travis E.L.: Radiation biology at clinically relevant fractions. in „Important Advances in Oncology", eds. by De Vita V., Hellman S., Rosenberg S.A., Philadelphia PA, Lippincott CA, 1991, pp 65-83;
6. Saunders M.I., Dische S., Grosch E.J. et al: Experience with CHART. Int. J. Radiat. Oncol. Biol. Phys. 21, 1991: 871-78; Radiother. Oncol. 25, 1992: 231-2410
7. Van der Schueren E., Van der Bogaert W., Vanuytsel L. et al: Radiotherapy by multiple fractions per day (MFD) in head and neck cancer: acute reactions of skin and mucosa. Int. J. Radiat. Oncol. Biol. Phys. 19, 1990: 301-11;
8. Wang C.C.: Local control of oropharyngeal carcinoma after two acceleratedhyperfractionation radiation therapy schemes. Int. J. Radiat. Oncol. Biol. Phys. 14, 1988: 1143-46;
9. Withers H.R., Maciejewski B., Taylor J.M.G.: Biology options in dose fractionation. BIR Report 19, 1989: 27-36