

## Original contributions

### What is the dose-limiting for altered radiotherapy for head and neck cancers – facts and doubts

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*Altered fractionation radiotherapy for head and neck produces locoregional benefit at the expense of an increased incidence and greater severity of acute reactions. This paper presents analysis of 21 data sets (2859 cases) including our own data of escalated and accelerated irradiation and aims to assess to what extent H & N mucosa is limiting to dose intensification by altered regimes.*

*The rate and speed of dose accumulation is the most important determinant for early reactions. The analysis shows that there is no single predictor for severity of acute mucosal reactions, and among many fractionation parameters maximal relative Accumulated Normalized Dose ( $rAND_{max}$ ) for week in which acute reaction reaches the peak of severity gives the best fit to all data, especially if  $\alpha/\beta$  ratio is lower than 10 Gy. It may suggest that H & N mucosa is more sensitive to change in dose per fraction as it is generally accepted.*

*Although mucosal reactions are more severe for altered fractionation regimes and troublesome for patients usually they are not beyond the limit of tolerance. After all, they are transient. It seems that the real dose-limiting factor is consequential late effects (CLE) which occur relatively early during follow-up and they may progress into permanent severe damage which significantly decreases the comfort and quality of life of the patients. For hybrids of accelerated – hyperfractionated regimes risk of CLE is low (<3.5%), however it increases to 15-20% for purely accelerated schedules. In order to avoid the risk of CLE, acute reactions should be regularly monitored during the treatment by precise and frequent scoring and recording of morphological changes and its severity.*

#### Jaki czynnik ogranicza dawkę w niekonwencjonalnej radioterapii raków głowy i szyi – fakty i wątpliwości

*Niekonwencjonalnie frakcjonowana radioterapia u chorych na raka regionu głowy i szyi zwiększa miejscowy zysk terapeutyczny kosztem zwiększenia częstości i nasilenia ostrych odczynów popromiennych. Aktualne opracowanie prezentuje analizę wyników 21 badań klinicznych (2859 przypadków) z uwzględnieniem badań własnych nad przyspieszonym frakcjonowaniem i eskalacją dawki całkowitej. Celem analizy jest ocena, w jakim stopniu ostry odczyn błony śluzowej w obszarze głowy i szyi jest czynnikiem ograniczającym intensyfikację dawki w zmiennych systemach jej frakcjonowania.*

*Wielkość i szybkość akumulacji dawki promieniowania jest najistotniejszym czynnikiem determinującym ostry odczyn popromienny. Wyniki badań wskazują na brak jednego i znamionego czynnika predykcyjnego dla nasilenia ostrego odczynu. Spośród licznych fizycznych parametrów frakcjonowanej radioterapii, najwyższą wartość wskaźnika względnej Znormalizowanej Dawki Akumulowanej ( $rAND_{max}$ ) w tygodniu, w którym ostry odczyn osiąga największe nasilenie, najsilniej koreluje z analizowanymi danymi klinicznymi, szczególnie gdy wskaźnik normalizacji  $\alpha/\beta$  ma wartość mniejszą niż 10 Gy. To sugeruje, że błona śluzowa w obszarze głowy i szyi może być bardziej wrażliwa na zmienność dawki frakcyjnej niż dotychczas sądzono. Pomimo, że ostre odczyny popromienne w trakcie niekonwencjonalnej radioterapii są bardziej nasilone i gorzej znoszone przez chorych, to nie podwyższają granicy tolerancji. Ponadto są one przejściowe. Wyniki przeprowadzonych analiz sugerują, że rzeczywistym czynnikiem ograniczającym frakcjonowanie dawki są „następowe odczyny późne” (CLE), które ujawniają się stonkowo wcześniej po zakończeniu leczenia i mogą ulec ewolucji w trwałe późne uszkodzenia popromienne, obniżające jakość i komfort przeżycia. Dla kombinacji przyspieszonego hiperfrakcjonowanego napromieniania ryzyko CLE jest niskie (3,5%), ale*

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*gwałtownie wzrasta do 15–20% dla wyłącznie przyspieszonych systemów frakcjonowanie. W celu zmniejszenia tego ryzyka, ostry odczyn popromienny powinien być regularnie monitorowany w trakcie leczenia poprzez precyzyjną i częstą ocenę ilościową zmian morfologicznych i stopnia ich nasilenia.*

**Key words:** altered radiotherapy, acute reactions, consequential late effects, dose – limiting factor

**Słowa kluczowe:** niekonwencjonalna radioterapia, ostre odczyny popromienne, następowe odczyny późne, czynnik ograniczający dawkę

## Introduction

Conventionally fractionated radiotherapy (RT) was considered as the major factor to decrease therapeutic gain. Combination of radiotherapy with surgery and/or chemotherapy may further increase the risk of late radiation morbidity. As altered fractionation schedules are more and more often explored in clinical studies, the application of more than one fraction per day of less than 2 Gy (hyperfractionation) produces increased sparing effects with regard to late normal tissue damage at the expense of an increased incidence and greater severity of acute mucosal reactions.

It has been claimed that acute morbidity becomes the main dose-limiting factor for altered fractionated schedules, yet this appears to be based on belief rather than on evidence-based conclusions.

### Acute mucosal radiation effects

Acute mucositis is the result of hypoplasia of the squamous epithelium due to sterilization of mucosal stem cells and inhibition of proliferation of transit cells. Fractionated irradiation leads to a gradual decrease in epithelial cell number, and when cell production can not keep up with cell killing partial or complete denudation develops presenting as spotted or confluent mucositis.

In conventional RT given in 1.8–2.0 Gy fractions, 5-times per week, confluent mucositis (CM) usually occurs within about 9 days after the dose of 20 Gy is accumulated [1]. The intensity of acute reactions reflects the balance between cell kill effect and the rate of repopulation of surviving stem cells. Once a peak of the CM is reached, further increase in dose and cell killing will not produce any further increase of the intensity of the acute reaction, but prolongs the duration of the CM and delays its healing.

The mucosa in the head and neck region rapidly sheds sublethal damage and it needs very little time for recovery. Ang et al. [2] has found that sublethal damage in lip mucosa is fully recovered within 3–4 hours and repair is faster than in late responding tissues [3]. Sublethal damage repair in acutely responding tissues is less important than repopulation which effectively balances the cell kill effect [1, 3–26]. Split – course schedules show rapid healing of the CM during 2–3 week break and mucosal reactions are generally milder in the second than in the first course of treatment. This can be ascribed to accelerated repopulation during and beyond the split. Withers et

al. [6] and Van der Schueren et al. [1] suggest there is no repopulation by clonogenic mucosal epithelial cells until day 12–14 of conventional irradiation, but thereafter between the third and seventh week mucosal isoeffect dose increases by about 1.0 Gy/day or even by 2.5 Gy/day during treatment breaks.

There is now a substantial number of studies using altered fractionation schedules (accelerated, hyperfractionated or its hybrids), and nearly all authors have reported an increased incidence and severity of acute mucosal reaction. It appears that the criteria of acute morbidity are not precise enough to determine the tolerability of any particular treatment schedule, and the majority of authors concentrate on grading differences of severity of usually tolerable normal tissue reactions to distinguish clinically tolerable from intolerable acute mucositis. Extensive clinical experience with different fractionation schedules permits the investigation of whether or not acute mucositis is truly dose-limiting for altered fractionated radiotherapy.

## Material and methods

The results of our own 2 studies [7, 8] and those of altered fractionation schedules which permit a reasonably accurate quantitative assessment of acute mucosal reactions taken from the literature were selected for the analysis comprising 21 data sets of 2859 cases of head and neck cancer. They were divided into 4 subgroups depending on fractionation schedule: accelerated (AF) – 5 data sets, hyperfractionation (HT) – 4 data sets; hybrid accelerated-hyperfractionation (AHF) – 12 data sets, and conventional fractionation (CF) includes cases of control arm in the randomized trials from 10 out of 21 data sets. Since it is rare, even in randomized trials, for all patients to receive exactly the same dose fractionation regimen, some liberty was taken in assigning mean doses and mean overall treatment times.

### Dose normalization

Because various schedules of dose intensity and fractionation are used in the analyzed sets of data absolute or mean values of total dose, dose per fraction and overall treatment time were used to normalized total doses (TD) and doses accumulated per week (AD) to equivalent values (NTD, AND) if given in conventional 2.0 Gy fractions using equation [3]:

$$NTD(AND) = TD_i (AD_i) [(\alpha/\beta + d_i)/(\alpha/\beta + 2.0)] - \gamma(OTT-14)$$

where  $TD_i$ ,  $(AD_i)$ ,  $d_i$  are a given total dose (accumulated dose per week) and  $\gamma$  dose per fraction, OTT is overall treatment time, and  $\gamma$  is a dose balancing mucosal repopulation per day. The  $\alpha/\beta$  ratio of 15.0 Gy was accepted for the calculation. Time correction factor was calculated based on the assumption the onset of mucosal repopulation on day 14 with the average rate ( $\gamma$ ) of 1.0 Gy/day in week 3 and 4, and 1.8 Gy/day thereafter [6].

Accumulate dose per week (AD), even if it is normalized (AND), changes in consecutive weeks of treatment, and allows to evaluate dose intensity only for a given specific fractionation schedules, but is it is generally useless and even may bias comparison with other altered schedules. Thus, a relative Accumulated Normalized Dose per week (rAND) was calculated for a given week (i) as a ratio of the AND<sub>i</sub> and AD<sub>C</sub> for conventional schedule of 70 Gy given in 35 fraction in 42 days (rAND<sub>i</sub>=AND<sub>i</sub>/AD<sub>C</sub>). For conventional standard the AD<sub>C</sub> corrected for repopulation and calculated for a consecutive weeks of treatment (AD<sub>C1</sub>, AD<sub>C2</sub>, AD<sub>C3</sub>...AD<sub>C6</sub>) was 10 Gy, 20 Gy, 23 Gy... 20.8 Gy respectively.

## End points

For the present analysis, only confluent mucositis (CM) (grade 4 EORTC or Dische score  $\geq 13$ ) was taken as severe acute reaction. Consecutive Dische scores [9] larger than 13 always represent the CM (with various rate of oedema, pain, bleeding and/or ulceration), however with increasing degree of functional morbidity. Incidence and severity of the CM was either clearly documented in tables or it has been determined from average graphical reaction patterns or deduced from objective and functional scores. To minimize errors many papers have not been accounted for the analysis because of unprecise or unknown scoring method

and/or qualitative characteristics of acute effects or it was impossible to reconstruct fractionation parameters.

Consequential late effects (CLE) is defined as a reaction morphologically-like typical late sequelae (massive fibrosis, epithelial, soft tissue or bone necrosis), but developing early (<6 months) after completing the treatment, and secondarily after very severe acute mucositis. If the CM healing occurred latency period was short (generally a few weeks) to the onset of CLE, but if it did not, the CM directly progressed into the CLE.

For the present analysis clearly documented CLE were included, and also these which characteristics of acute reaction, the nature and the onset of sequelae likely allow to suspect they are consequential.

## Statistical methods

Data points representing the incidence of CM weighted by the number of cases were plotted against AND and rAND values, and dose response curves were estimated by logistic regression. The curve which gives the best fit to data points scattergram was determined by maximum – likelihood estimation and chi-square likelihood-ratio test was applied to calculate the goodness of the fit. To estimate dose-time curve for acute mucosal reaction the NTD values for the CM in the range of 40-90% reported in 13 data sets were plotted against overall treatment time.

**Tab. I. Incidence of severe confluent mucositis (CM, IVo EORTC) in relation to fractionation characteristics**

Series schedule	No pts.	NTD <sub>2.0</sub> (Gy)	OTT (days)	TI (hours)	AND <sub>1</sub> (Gy)	rAND <sub>max</sub> (*)	CM	CLE	Authors
<b>AF – Accelerated</b>									
a. t.i.d	22	54.0	12	4	30.0	2.7 <sub>(2)</sub>	100%	55%	Paracchia et al. [10]
b. t.i.d. (3d/wk)	89	58.7	24	4	16.0	1.8 <sub>(4)</sub>	90%	-	Lamb [11]
c. b.i.d.	82	66.0	25	6	20.0	2.64 <sub>(4)</sub>	70%	5%	Jackson [12]
d. escal.-CB (b.i.d.)	18	70.0	35	6	10.0	2.65 <sub>(5)</sub>	90%	10%	Kaanders [13]
e. q.d. (7d/wk.)	50	70.0	35	24	14.0	2.99 <sub>(5)</sub>	82%	22%	Maciejewski [7]
<b>HF – Hyperfractionated</b>									
f. b.i.d. RTOG 83-13	447	64–73	38-42	4–8	11.4	1.42 <sub>(6)</sub>	40%	-	Cox [14, 15]
g. b.i.d. RTOG 79-13	187	70.3	49	3–6	8.9	1.3 <sub>(3)</sub>	23%	-	Marcial [16]
h. b.i.d.	41	68–76.6	45	4	11.4	1.3 <sub>(3)</sub>	30%	-	Wend [17]
I b.i.d. EORTC 22791	325	76.4	49	6	10.9	1.57 <sub>(7)</sub>	67%	-	Horiot [18]
<b>AHF – Accelerated hyperfractionated</b>									
k. t.i.d.	11	40.5	12	4	20.2	2.02 <sub>(2)</sub>	100%	-	Awward [19]
l. tid CHART (7d/wk)	552	52.4	12	6	30.5	2.62 <sub>(2)</sub>	73%	-	Dische [20]
m. t.i.d.	19	50.0	14	3	25.1	2.51 <sub>(2)</sub>	100%	- 11%	Svoboda [5]
n. e.i.d. – S	173	67.3	26	2	33.6	3.36 <sub>(1)</sub>	100%	-26%	N'guyen [21]
o. b.i.d. PMH	109	56.1	28	6	14.0	1.61 <sub>(4)</sub>	63%	-	Cummings [22]
p. t.i.d. – S EORTC 22851	214	70.3	34	4–6	23.4	1.86 <sub>(4)</sub>	80%	13%	Horiot [23]
r. b.i.d.-escal.-S	16	68.6	35	6	15.6	2.11 <sub>(5)</sub>	100%	-	Maciejewski [8]
s. b.i.d. – escal.	12	73.4	35	6	13.8	2.71 <sub>(5)</sub>	100%	-16%	Harari [24]
t. b.i.d. – S	28	67.5	40	6	17.8	2.71 <sub>(5)</sub>	96%	7%	Delaney [24]
u. b.i.d. – CB	43	70.8	42	6	8.89	1.51 <sub>(6)</sub>	81%	-	Ang [25]
w. b.i.d. – S	321	65.6	42	4	15.6	1.56 <sub>(2)</sub>	66%	-	Wang [26]
y. b.i.d. – CB	100	69.6	45	6	13.5	1.46 <sub>(3)</sub>	60%	-	Johnson [27]
<b>Conventional</b> (b,d,e,f,g,h,i,l,o,p)		66–72	44–49	24	8.89–10.0	1.0 <sub>(1-8)</sub>	30% (10–55%)		

[NTD<sub>2.0</sub> – Normalized Total Dose if given in 2.0 Gy fractions; AND<sub>1</sub> – Accumulated Normalized Dose in week 1, rAND<sub>max</sub>(\*) – relative AND with maximum value in week (\*); CM – confluent mucositis; CLE – consequential late effect; fractionation: q.d. – once-a-day; b.i.d. – twice-a-day; t.i.d. – trice-a-day; e.i.d. – eight times a day; S – split; CB – concomitant boost]

**Tab. II. Average relative Accumulated Normalized Dose per week (rAND) in relation to the mean incidence of confluent mucositis (CM) and the risk of CLE for four different fractionation regimes**

Fractionation	rAND <sub>max</sub>	CM incidence % ± (SD)	CLE risk	Tolerance
mainly conventional (CF - HF)	1.26 (1.0-1.51)	30% (±12.5%)	0%	tolerable
mainly hyperfractionation (HF - HAF)	1.69 (1.45-1.93)	62% (9%)	0%	troublesome but tolerable
hybrid accelerated-hyperfractionation (AHF)	2.2 (1.94-2.46)	82% (±13%)	≤3.5%	severe (delayed healing) but still acceptable (small risk of CLE)
purely accelerated (AF)	2.75 (2.4-3.0)	90% (±8%) p<0.001	≈14% (8-20%)	always severe and prolonged with delayed healing. dose-limiting (high risk of CLE)

## Results

### Acute mucositis - incidence and severity

Incidence of the CM in relation to various altered fractionation schedules is presented in Table I. At the first glance, this table shows an increased incidence of the CM in altered schedules compared with conventional treatment. For the conventional 2.0 Gy fractionation regimen, a mean value of the CM incidence of 30% (±12.5%) was calculated (Tab.II). For HF schedules the rate of CM was about 2 times higher, and 2.5-3 times higher for hybrid AHF and purely AF respectively (Fig. 3). The CM rates for the last two schedules reflect an increasing risk of the CLE.

### Accumulated Dose per week (normalized and relative)

The assessment of the dose-effect relationship for acute normal tissue reactions is complicated by the fact that

the acute reaction which has been influenced by a certain radiation dose will only appear several days or even weeks later, at which time a much higher dose has already been accumulated. Previous analysis [24] of acute mucosal reactions in a large group of head and neck cancer cases treated with conventional and altered radiotherapy showed that CM occurred more severe after higher doses per fraction. They were, consequently, more frequent with a higher rate of dose accumulation. This observation suggests that the accumulated dose per week could be used as a parameter to characterize the association between dose intensity and CM incidence. Since during the first week of RT the discrepancy between cell production and cell killing is the greatest the choice of the AND<sub>1</sub> in the first week seems to be logical. Figure 1 A plots scattergram of the CM rates from Table I against the AND<sub>1</sub>, and it shows no correlation between the AND<sub>1</sub> values and the CM and CLE. High rates of both events equally correspond with the AND<sub>1</sub> of 10 Gy and 30 Gy as well. It clearly shows that in altered fractionation schedules the AND<sub>1</sub> (or absolute AD<sub>1</sub>) is not a good predictor for the

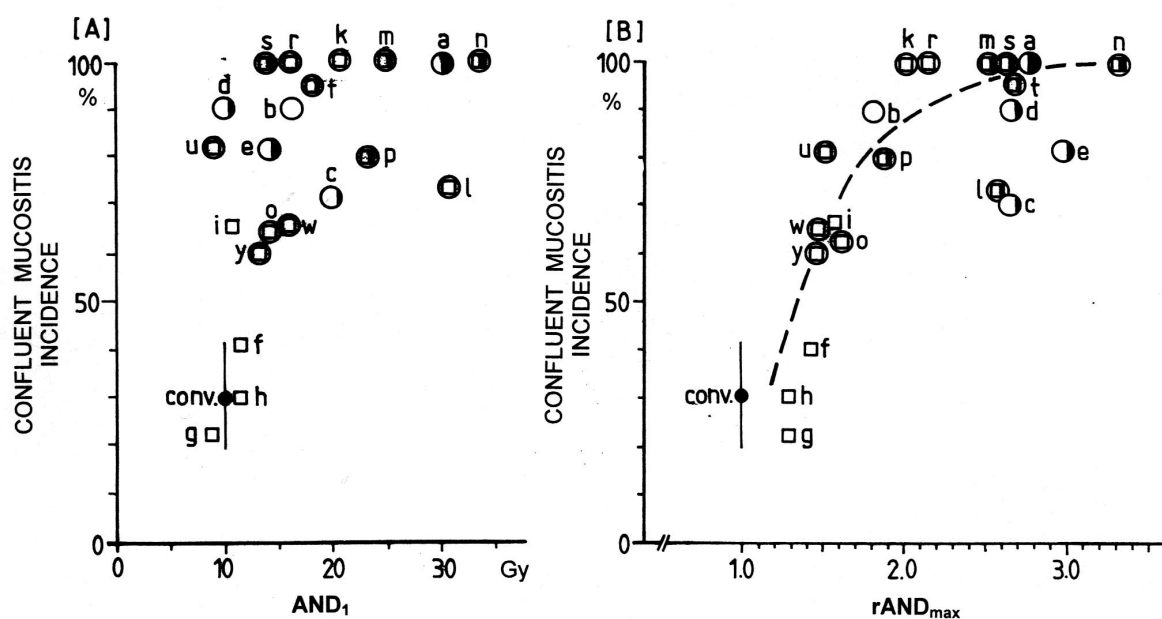


Fig. 1. Scattergrams of confluent mucositis (CM) depending on (A) Accumulated Normalized Dose in the first week of treatment (AND<sub>1</sub>); (B) relative AND<sub>max(i)</sub> which reaches maximum value in week (i). [Characters correspond with data sets listed in Table I; circle - AF schedule; square - HF schedule; square within the circle - AHF schedule; small black circle - conventional schedule; black area within the symbol corresponds with the risk of CLE]

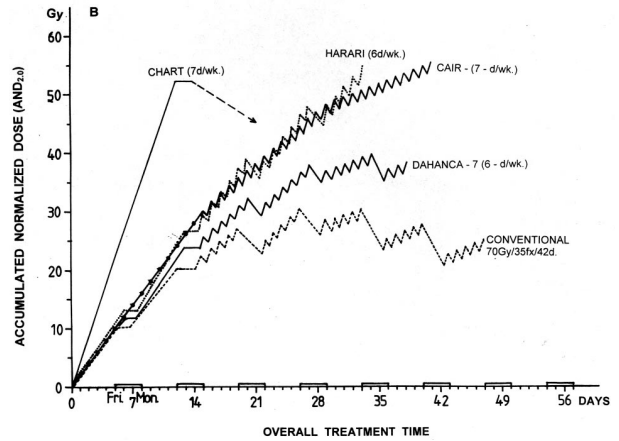
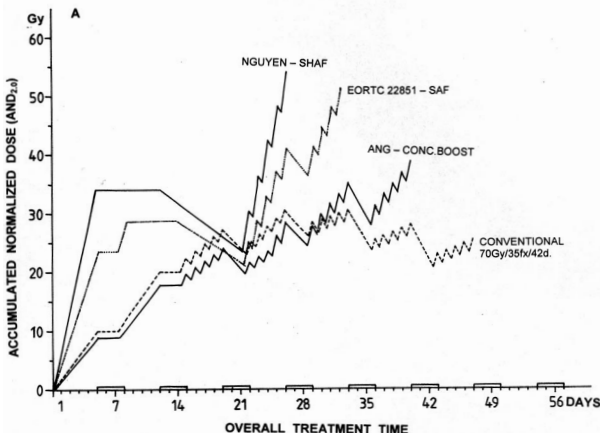


Fig. 2. Normalized Dose accumulated during treatment time (A) for 3 AHF schedules compared to conventional standard; (B) for 4 AF schedules

risk of CM and CLE, because the AD may not be constant during the consecutive weeks of treatment.

It can be clearly observed if the intensity of dose accumulation is evaluated week by week during the treatment (Fig. 2 A and B). If the dose accumulation is accounted for the effect of mucosal repopulation for conventional RT the AND<sub>5</sub> and AND<sub>6</sub> values are lower than that for the first two weeks of RT. It convincingly supports the Fletcher [28] observation of mucosal healing during the last week of treatment in 75% of cases treated with conventional RT and dose per fraction equal or lower than 2.0 Gy. In contrast, for altered fractionation the dose is continuously accumulated in the rate higher than the effect of mucosal repopulation and the AND for the last two-three weeks of treatment is higher than at the beginning, which the AND<sub>1</sub> value might be totally misleading for because it is similar to that for CF or even smaller if concomitant boost schedule is used (Fig. 2A). For aggressive accelerated-hyperfractionated schedules (Fig. 3B) lasted longer than two weeks, even one-two week break does not really change intensity of dose accumulation.

For this reason the AND values for week 1, 2, 3, etc. and AND<sub>max(i)</sub> for the week (i) in which it has reached the highest values were accounted for to the present analysis.

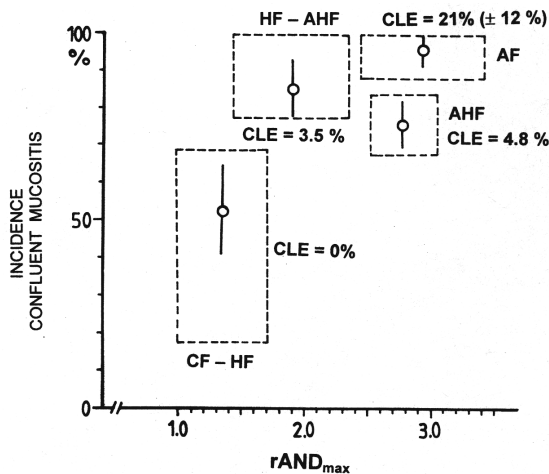


Fig. 3. The average incidence of CM and the risk of CLE for different altered fractionation schedules depending on rAND<sub>max</sub>.

Figure 1 B plots a scattergram of the CM rates from Table I against rAND<sub>max</sub>, and the respective regression curve was estimated. The correlation analysis showed that among the AND parameters the rAND<sub>max</sub> gives the best fit to the analyzed data (Tab.III). This suggest that for altered fractionation schedules there is no single and constant week in which the respective AND value gives the best characteristics of the risk of CM for but it differs depending on the intensity of dose accumulation, and the highest rAND value (rAND<sub>max</sub>) seems to be the best practical choice.

Tab. III. Goodness of the fit to the CM rate depending on the AND parameter

Parameter	Chi-square value
AND <sub>1</sub> *	601
AND2 value:	
→ ∞	694
= 10 Gy	719
= 4.0 Gy	739
= 2.0 Gy	746
rAND <sub>max</sub> (**)	801

\* chi-square values for AND<sub>3</sub>, AND<sub>4</sub>, AND<sub>5</sub> were lower than for AND<sub>1</sub>, and then they are not listed in the table

\*\* week in which rAND reached the highest value

The majority of data points close to the regression curve (Fig. 1 B) represent highly intensive treatments. For rAND<sub>max</sub> higher than 1.7 the CM rate has always been above 60%. In all split-course AHF schedules, except EORTC 22851, the incidence of CM is related to the dose intensity throughout the first course before the break. Acute mucosal reactions were never more severe in the second course than in the first part of treatment, and they were generally well tolerated by the patients.

There were also evident fractionation traps, especially N'guyen study [21]. The authors have used only 0.9 Gy per fraction trying to keep treatment safety. However, by using 8 fractions per day with only 2 hours interfraction intervals the rAND<sub>max</sub> was 3.36 and even 2-week break between two one-week courses of such in-

tensive irradiation (Fig. 2A) did not counterbalance deep and disastrous mucosal denudation which resulted in dramatic treatment outcomes of 100% of severe CM and 26% of CLE.

Van der Schueren et al. [1] study on 4 different altered fractionation schedules showed that when the  $AND_{2(max)}$  decreased from 46.8 Gy (sch.I) to 29.3 Gy (sch.II) the incidence of CM decreased from 100% to 66%, and reactions were less severe and healed faster than that during conventional RT with  $AND_2$  of 20.0 Gy. They always subsided before the second course of irradiation was started. When the  $AND$  of 16.0 Gy (in 2 days) was followed by the 12 days breaks (sch.IV), the majority of patients did not reach confluent mucositis although this  $AND_2$  was repeated three more times.

The importance of dose intensity and of the position of a concomitant boost (CB) during the treatment course has been documented by Ang and Peters [25]. When CB is delivered during the last 2-2.5 weeks of treatment the  $AND_{(1,2)}$  is very misleading because it suggests that the schedule is even less intensive than conventional RT, whereas the  $rAND_{max}$  has reached the highest value of 1.51 in the last week of treatment, and it resulted in 81% of CM. The same situation was noted for 3 studies using dose escalation [8, 13, 24], where the  $rAND_{max(5)}$  in week 5 in the range of 2.11–2.71 has corresponded with almost 100% incidence of the CM and 10-16% rate of consequential late effects in the two out of these studies. In all these studies no significant increase in the severity of acute mucosal reactions during the first four weeks of treatment was observed. It was postponed to the end of therapy, since the dose was not intensified until the fourth week. Thus, for the CB and escalated altered schedules with the high dose intensity only in the last part of treatment the  $AND_1$ ,  $AND_2$  or  $AND_3$  seem to be a week predictor for the risk of CM.

Table II and Figure 3 shows that  $rAND_{max}$  significantly ( $p < 0.001$ ) correlates with the incidence of the CM and, in fact, only hybrids of intensive accelerated hyperfractionation (AHP) and mainly purely accelerated (AF) schedules strongly correlate with the risk of consequential late effects.

#### Alpha/beta ratio

An alpha/beta ratio reflects how sensitive are irradiated tissues (tumours) to the change in dose per fraction. With the data available, it is impossible to estimate directly an  $\alpha/\beta$  value for acute confluent mucositis, since there is no way to determine what part of the total dose causes the peak of acute reaction. However, it was found that among  $AND$  values normalized for different  $\alpha/\beta$  ratios that for  $\alpha/\beta$  of 2.0 Gy gives the best fit to the data points (Tab.III). This finding is indirectly supported by our observations in the CAIR trial [7]. When the fraction size was reduced by 10% (from 2.0 Gy to 1.8 Gy), the incidence of CLE decreased from 22% to zero and the rate of CM decreased from 83% to 62%. It may suggest that oral mucosa is more sensitive to even small changes

in fraction size than it was generally assumed, and consequently, it may suggest  $\alpha/\beta$  value lower than 10 Gy. However, the influence of prolonged overall treatment time should not be ignored.

#### Dose-time relationship

Since the accuracy of the total dose determined for a specific end-point in a given overall treatment time is uncertain, it is very difficult to construct dose-time curves for acute mucositis. A theoretical dose-time curves (Fig. 4, dotted line) was drawn based on the assumption proposed by Withers et al. [6] that 34.0 Gy in 2.0 Gy fractions given in about 12 days produces an acute mucositis of almost the same severity as 70.0 Gy in 35 fractions in 7 weeks and 50.0 Gy in 26 fractions in 4 weeks. This theoretical curve is compared with the curve estimated for the analyzed data sets (Fig. 4, solid line). The slope of this curve is steeper than that proposed by Withers, and suggest that repopulation of mucosal epithelial cells is able to compensate on average the effect of about 1.5 Gy/day after 12–14 days of fractionated irradiation, instead of 1.0 Gy/day estimated by Withers.

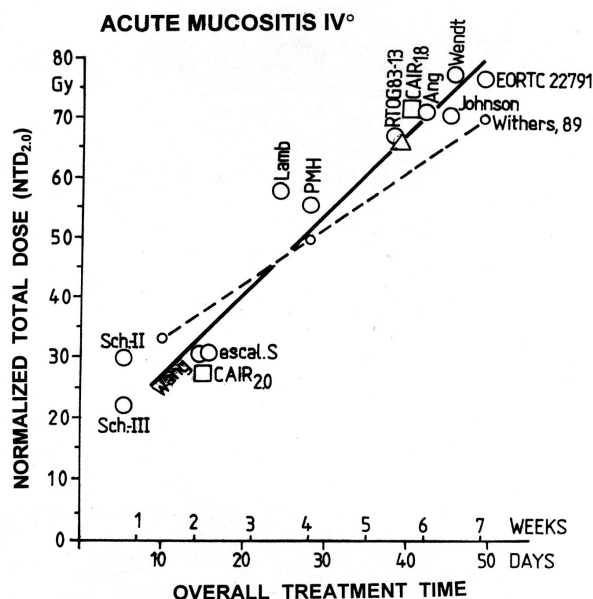


Fig. 4. Iso-effective dose-time curve for confluent mucositis (CM). Black circles and dotted line represent theoretical curve proposed by Withers et al. [28]

Although many variables which are independent of dose fractionation (i.e. individual radiosensitivity, size and location of treatment volume) could bias this estimation, the dose-time curve for the acute effect on Figure 4 provides a reasonable approximation of the effect of mucosal repopulation. Practically, it may help to calculate an “effective total dose” producing the specific morphological damage of mucosa which, for example, for total physical dose of 70.0 Gy given in 40 days would be 44.0 Gy (assuming repopulation rate of 1.0 Gy/day) or only 31.0 Gy (for a repopulation rate of 1.5 Gy/day). The-

Tab. IV. Consequential late mucosal reactions (CLE)

AUTHOR	dose per fraction	interfraction interval (hours)	rANDmax	CLE
N'guyen et al. (n)	0.9 Gy (8 fr/d)	2	3.36 (1) 2.05 (2)	26% (80%?)
Paracchia et al. (a)	2.0 Gy (t.i.d.)	4	2.7 (2)	55%
Maciejewski (e)	2.0 Gy (7d/wk, q.d)	24	2.99 (5)	22%
Harari (s)	2.0 Gy (b.i.d.-escal)	6	2.71 (5)	16%
Horiot (r)	1.6 Gy (t.i.d., split)	4	1.86 (4)	13%
Svobada (m)	1.7 – 2.3 Gy (t.i.d.)	3	2.51 (2)	11%
Kaanders (d)	2.0 Gy (b.i.d.-escal)	6	2.65 (5)	10%
Delaney (t)	1.8 Gy (b.i.d.)	6	2.71 (5)	7%
Jackson (c)	2.0 Gy (b.i.d.)	6	2.64 (4)	5%
Maciejewski (e)	1.8 Gy (7d/wk, q.d.)	24	2.65 (5)	0%
AHF-CF (b,f-l,o,r, u-y)	1.6 – 2.0 Gy (b.d., q.d.)	> 6	< 2.0 (3-5)	0%

se values are lower than the 54.0 Gy given in 12 days. Therefore, one may expect less severe acute mucosal reaction for conventional irradiation than for 54 Gy in 12 days, as it was in the case of CHART.

#### Consequential late effects

According to Peters et al. [5], severe mucosal denudation with no sufficient reserve of epithelial cells to heal and insufficient migration of the surviving cell from margins of the field into the irradiated area may cause gradual progression of acute reaction into consequential late effect (CLE) occurring relatively early after the end of treatment.

Table IV and Figure 5 show an increasing rate of the CLE with higher dose intensity and shorter interfraction interval. The most dramatic series of CLE reported by N'guyen [21] and Peracchia [10] may be related to very short interfraction intervals and thus, to accumulation of incomplete repair of sublethal damage. For the

majority of hybrid AHF schedules the CLE has been reported incidentally, or indirectly described as it is in the case of the EORTC 22851 trial [23].

Kaanders et al. [24] suggest that in addition to dose intensity factors such as field size, anatomical site and the performance status of the patients may also play an important role in the development of CLE. Our results on the CAIR trial support this suggestions showing that combination of high maximal score of the severity of acute reaction and its long duration with delayed healing were significantly associated with the CLE, rather than just one of them (Tab.V). The CLE always developed within a small field which had been irradiated 7 days a week, and never within a larger one receiving 5 day a week treatment. It is important that a 10% decrease in fraction size (from 2.0 Gy to 1.8 Gy) without any other changes in fractionation parameters reduced the CLE risk from 22% to zero, and no more CLE occurred.

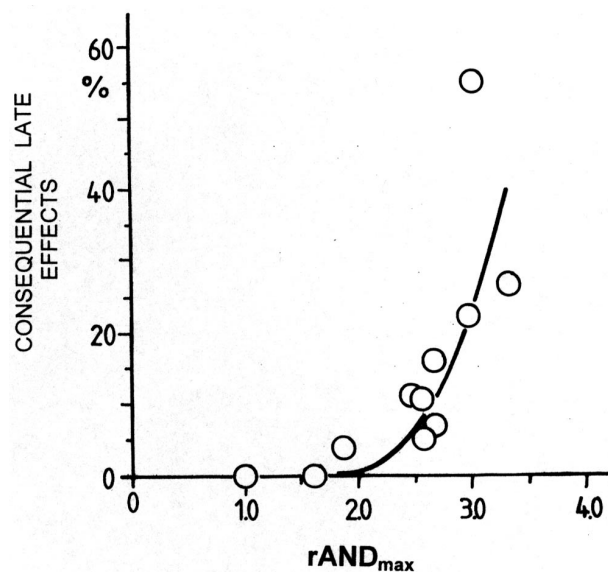


Fig. 5. Risk of consequential late effect (CLE) depending on the rAND<sub>max</sub> values

Tab. V. Risk factors for consequential late effects (according to Maciejewski et al. [7])

Factors	CLE (-)	CLE (+)	Significance
Maximum Dische score	15	18	0.04
Duration (weeks) of score >15	1.8	3	0.06
Average score during the period 3–11 wks	9.5	13	0.06
Large field size (cm <sub>2</sub> )	118 (89-118)	132 (117-144)	0.01
Hb loss (g/dl) during RT	0.7 (0.7 – 2.2)	1.75 (1.2 – 2.8)	0.02
Weight loss (kg) during RT	≤3	≥6	0.03

(factors such PFS, T-stage, total dose, overall treatment time did not reach the level of significance)

## Discussion

In radiotherapy, locoregional benefit should be balanced against any acute and late normal tissue damage. Late effect seriously threaten the quality and length of life, whereas acute reactions might require a break during the treatment, and thus may threaten the chance of tumour control. The latter point becomes crucial when the intensive altered fractionation schedules are used.

### Incidence and/or versus severity

The present results show a significant increase the CM incidence by 2-3 fold for purely accelerated schedules, but the difference between AF and AHF, and between CF and mainly HF was less pronounced and not significant (Tab. II). Does this mean that a high CM incidence is dose-limiting? The incidence does not closely correlate with the severity of CM. Although the rate of severe dysphagia requiring tube feeding is about 2 times higher in AHF and AF than in CF and HF regimes, intolerable CM generally occurred in short intensive AF and in some escalated regimes [10–13, 24]. In contrast, split-course AHF treatments [8, 26], except EORTC 22851 [23], were generally well tolerated. Then, more frequent CM does not automatically mean more severe event. Even 100% incidence of CM did not necessarily required a break during RT and may be quite well tolerated by the patient.

The CM incidence depends on the rate of dose accumulation, at least during the first two weeks of treatment, whereas the severity of CM depends less on dose-fractionation, but other factors such as volume, anatomical site, patient performance status, infections and some diseases producing mucosa degeneration and/or atrophy prior to cancer development may play an important role. The volume effect is well recognized although it is not accurately measured. Although others factors are often ignored and not accounted for the analysis, the CM rates were more accurately quantified than their severity.

The present comparison might be and probably is hampered by many other uncertainties. Data collected for the present analysis, although often cited in the literature, came over two decades from a variety of centres, and thus, are likely biased by many between authors differences, particularly in definition of the end-points. The term “confluent mucositis” was used in some papers [27] as a grade III, in another as a grade IV [1], or even grade V [11]. In Marcial and Wendt studies [16, 17], the CM rates seem to be underestimated because they are mainly referred to the patients who required nasogastric tube feeding. Only 5 of 21 data sets present individual or average severity-time patterns which allow accurate quantitation.

Further comparison shows that for almost identical fractionation patterns (Tab. I-sets: l vs. a, and u vs. y) quite different CM rates were recorded. It might be explained by the difference in interfraction intervals. On the

other hand, difference in the CM rate in three escalated regimes (Tab. I-sets: d, r, s) could be the results of different dose intensity. Despite many uncertainties in the majority of HF and of many AHF regimes the rate and severity of the CM did not alter the feasibility of fractionation protocols, and unexpected breaks during the treatment were rare. Generally, in the HF sets about 16–20% patients required tube feeding. The CM in the AHF and AF sets was significantly more frequent and severe than in the former sets, especially for concomitant boost, continuous regimes without split and with short overall treatment time. In these series severe dysphagia generally occurred in 25–52% of patients and 30–35% of them required tube feeding. Complete CM healing was delayed up to 8–10 months after the end of RT or even longer when pure AF regimes were used.

Van der Schueren et al. [1] and Wang [26] have noted that in altered split-course regimes weight loss was not important. In contrast, in our CAIR trial strong correlation between weight loss and severity of the CM was observed [7]. Weight loss of more than 5 kg occurred in 54% of patients with very severe CM lasting longer than 3 weeks, and some of these patients developed consequential late effects.

Do we have predictors of the risk and severity of CM?

In altered radiotherapy currently tested various parameters are strongly and usually simultaneously changed. Thus, it is difficult to estimate the relationship between the acute response of normal tissue and the dose intensity. Moreover, even if accumulated dose per week is normalized to 2.0 Gy fraction regime it usually is not constant during treatment. The  $AND_1$  or  $AND_2$  (the first two weeks of RT) may strongly correlate with the risk of CM only if intensive dose-fractionation is concentrated in the initial part of treatment before split (CHART, CB, EORTC 228451) or when the OTT is very short (Parachia, Awward, Svoboda). This correlation becomes weak and misleading if the dose intensity increases continuously (CAIR) or at the end of treatment (Harari, Kaanders).

The present analysis shows that best fit to the CM rates gives the relative  $AND_{(max)}$  in the week in which it reaches the highest value, and probably for  $\alpha/\beta$  value lower than 10.0 Gy. Heterogeneity of data sets and fractionation parameters may bias the present results, and thus, the low alpha/beta value should only be interpreted as a suggestion, not as a definitive value. However, support for this suggestion comes from the CAIR trial where small reduction in fraction size from 2.0 Gy to 1.8 Gy decreased the 22% risk of CLE to zero. Although the present results suggest that the  $rAND_{max}$  might be practically a useful parameter it seems there is no single predictor for the risk of severe CM. Combination of a few items ( $rAND$ , time-speed to reach a peak of severity and its duration, weight and Hb loss, treatment volume) might be predictable rather than just one of them.



What should be considered as a dose-limiting?

The most important point is „what is the battle about”, that means what we understand as a tolerance-limit for acute responding tissues. Is it prolonged severe confluent mucositis, delayed healing or severe functional effects as dysphagia requiring tube feeding? There is convincing evidence that this is not the case. Although confluent mucositis is a frequent complication during radiotherapy and it is associated with very unpleasant symptoms such as pain or dysphagia, it usually is manageable and certainly not beyond the limit of patient tolerance as the price for cure. Above all, it is transient. The term tolerance defines the response of the patient to acute or late normal tissue reactions. Thus, the increased severity of the injury and the reduced tolerance reflects the response of the patient, and not necessarily the response of the tissue [24]. Therefore, the clinically relevant criterium of acute, sub-acute tolerance after radiotherapy of head and neck cancers should not be determined by confluent mucositis (whatever its severity) but by consequential late effects which have to be avoided, if possible. The CLE is clearly beyond the limit of tolerance because it is difficult to manage therapeutically and may lead to permanent morbidity. Present results demonstrate that among various altered fractionation schedules and the majority of AF regimes and only some of the AHF hybrid might be at the high risk of CLE and the rAND higher than 2.6 could be considered as dose-limiting predictor for unacceptable risk of the CLE (Tab. II, Fig. 1B).

High the rAND value may reflect fast increase in the severity of acute reaction toward the early peak of confluent mucositis with the progress in dysphagia, pain on swallowing and weight loss. In such cases the risk of CLE might be decreased by early administration of systemic corticosteroids, antibiotics, parenteral nutrition or acute reaction modifiers. Above all, in order to recognize such danger situation for the individual patient and to establish the limitation of altered fractionation regime precise quantitative and regular scoring of acute reactions is needed. Our experience with the Dische scoring system [7–9] shows its practical advantages because it places emphasis on both functional disorders and morphological changes. However, the use of an appropriate scoring system does not by itself solve the problem of assessment of the limits of tolerance, unless acute reactions are regularly scored during the treatment and thereafter, until complete healing is achieved.

How the game should be played

The present analysis shows that the mucosal epithelium is able to compensate the effect of 1.5 Gy/day between the second and seventh week of treatment and it is higher value than 1.0 Gy/day postulated by Withers et al. [6]. It likely seems that during last 2–3 weeks of 7-week schedule it could even increase to 1.8 Gy/day and may be to 2.5 Gy/day during the weekends. Thus, mucosal repopula-

tion is more effective and begins earlier than that by surviving tumour clonogens. If one wishes to use intensive dose fractionation schedule, the longer dose is delivered difference between tumour and mucosa repopulation becomes smaller and smaller.

Kaanders et al. point out that in most patients the mucosa can not compensate dose greater than 10 Gy per week [24]. However, it does not seem true. In the CHART the AND<sub>1</sub> of 30.5 Gy or 23.4 Gy in the EORTC 22851 trial did not result in extremely high incidence of CM but the former schedules lasted only 12 days, and in the second one after the first two weeks of irradiation 12-14 day break was introduced. In contrast, the AND<sub>1</sub> of 14 Gy in CAIR trial was too much [7]. It may suggest that the most important is „how the game is played”, it means, how fast and in what rate the dose is accumulated during the treatment.

Analyzing advantages and disadvantages of the EORTC 22851 trial [23] and the CAIR [7]. Kaanders et al. [24] concluded than none of many clinical and physical parameters could satisfactorily explain the greater acute toxicity of CAIR. However, despite the fact that the EORTC-AHF was the split-course schedule, the most important difference is that it was “weekend-free” treatment, in contrast to CAIR which was “weekend continued”. The regular 24-hours intervals between 2.0 Gy fractions continued over 5 weeks were probably not long enough for effective compensation of progressive denudation of epithelium leading to persisted severe mucosal reaction finally progressed into the CLE in 22% of patients. Thus, regular weekend breaks and split periods likely allow mucosa repopulation to compensate radiation injury. Mucosa repopulation during short or longer breaks seems to be more effective than during the irradiated weekdays. In contrast, 6–7 days per week schedule results in regular continuous dose accumulation (Fig. 2B), and in week 4 of treatment the AND higher than 40 Gy strongly correlates with a high risk of dose-limiting consequential late effect. It corresponds with about 60 Gy of uncorrected total dose. Thus, 60 Gy in 4–5 weeks can still be tolerated [24], and there is no reason to shorten the OTT to 1.5–2 weeks, because the reduction in total dose neutralizes the expected local tumour control.

It has to be kept in mind that a severity of acute effects strongly correlates with tumour control. This is not surprising since they both are a function of dose accumulation. Although, this observation may seem obvious, the converse is of practical significance; mild acute reactions during RT may be related to an increased risk of treatment failure. Thus, optimal therapeutic gain might be achieved if altered fractionation regimes produce acute mucosal reaction at the level as high possible but still tolerable by the patient.

## Conclusions

Although it is necessary to be aware of the limitations of the present analyses and of some uncertainties regarding

the precise averages, the following implications can be formulated:

1. Assessment of frequency and severity of acute mucosal reactions in radiotherapy, at least for head and neck region, requires regular recording of morphological and functional effects until complete healing is achieved using the accurate scoring system, and reaction pattern should be plotted for each individual patient.
2. It seems that maximal relative accumulated normalized dose per week (rADMmax) could be a good estimator of the incidence of confluent mucositis, and partly of its severity.
3. It is important to be aware of the risk of consequential late effects which are the true dose-limiting complications of radiotherapy of head and neck cancer, not, however, transient confluent mucositis.
4. The tendency of doctors to be kind to patients by minimizing acute toxicity is likely to be unkind to them by decreasing probability of tumour control.

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