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Original contributions

To the ranch and back – benefits vs. costs in altered radiotherapy for head and neck cancers*

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Aim of study. To analyze the benefit and costs of clinical trials on altered fractionated radiotherapy for head and neck cancer. Doubts and uncertainties concerning overall therapeutic gain are discussed.
Material and methods. Data sets of 12 clinical trials most often cited in the literature, including all together 4682 cases of head and neck cancer are included into the analysis. They represent all tumours stages and sites and wide variety of altered fractionation schedules, i.e. accelerated (AF), hyperfractionated (HF) and hybrid accelerated hyperfractionated (AHF) regimes. At least 3-year locoregional control and the incidence of consequential late effects and true late complications are used as end-points for benefits and costs respectively.
Results. In some studies AF/AHF regimens were superior for advanced tumours (CHART, EORTC 22791) but not for T2, whereas in others significant benefit was noted for tumours smaller than 4 cm (PMH). Various uncertainties arise concerning selection and dosimetric biases. Interpretation of the costs is even more uncertain than that of the LRC benefit. Grade 2 and 3 late effects (LE) are often groupped together, several events may occur in the same patient. Whilst the LRC is quantified as actuarial, the LE is presented as a crude data. Moreover, consequential late effects can mostly be only deducted from the published results. Thus the costs are generally underestimated. For some trials (Cairo, EORTC 22851), LRC benefit and the TG is apparently positive, but precise quantitation of LE and CLE makes some trials negative. Final analysis suggests that an overall therapeutic gain is moderate in the range of 0-15%. Analysis of the Normalized Total Doses corrected for changes in fraction size and overall treatment time and recalculated for 50% probability of the LRC (NTCD5o) shows an average of 0.6 Gy/day balancing tumour clonogen repopulation might be to low, and it can increase to 0.85 Gy/day or even 1.1-1.2 Gy/day during the weekends. Furthermore, it seems that the lag period could be shorten to 14-21 days.
Conclusions. The results convincingly suggest that the TG may likely be seriously constrained by the intention to use total doses limited to the level of acute tolerance, which however does not seem to be dose-limiting. Intensive regimen with twice-a-day fractions, and without or slight reduction in total dose can only be delivered by escalating the dose beyond working days, that means, including weekends. DAHANCA-7 and CAIR trials support this concept. However, for such intensive treatment the safe window is narrow, and small change in time or dose can shift enhanced but tolerable mucosal morbidity towards very severe and intolerable late complications. Despite two decreases of extensive studies the question what should be the best altered regimen for specific tumour site and stage still remains widely open.

"To the ranch and back" – korzyści i koszty (powikłania) niekonwencjonalnej radioterapii chorych na raka regionu głowy i szyi

Cel pracy. Ocena zysku terapeutycznego i kosztów (powikłań) niekonwencjonalnej radioterapii u chorych na raka regionu głowy i szyi oraz krytyczne dyskusje wyników kontrolowanych badań klinicznych.
Materiał i metodyka. Materiał obejmuje 4682 przypadki raka regionu głowy i szyi o różnej lokalizacji i zaawansowaniu, włączone do 12 najczęściej kontrolowanych badań klinicznych. Oceną objęto różne systemy frakcjonowania dawki, tj.

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przyspieszonego (AF), hiperfrakcjonowanego (HF) i hybrydowego (AHF). Jako kryteria zysku i kosztów przyjęto odpowiednio 3-letnie wyleczenie lokoregionalne oraz częstość następowych odczynów późnych (CLE) i typowych późnych powikłań (LE). Wyniki. W niektórych trialach frakcjonowanie AF/AHF przyniosło zysk terapeutyczny w grupie zaawansowanych raków, przy braku zysku w stopniu TZ (CHART, EORTC 22791), podczas gdy w innym trialu (PMH) znamienny zysk terapeutyczny odnotowano w grupie guzów o średnicy <4 cm. Szereg wątpliwości dotyczy błędów selekcji i dozymetrycznych. Ocena powikłań dostarcza więcej wątpliwości niż w przypadku zysku LRC. Późne efekty 2 i 3 stopnia są często oceniane łącznie, a kilka różnych powikłań może występować u jednego chorego. Późne odczyny są podawane w wartościach bezwzględnych, podczas gdy LRC oceniane jest metodą aktualizacji. Ponadto ryzyko odczynów następczych można jedynie dedukować z opublikowanych wyników. A zatem LE (koszty) są generalnie niedoszacowane. W niektórych trialach (Cairo, EORTC 22851) zysk jest pozornie dodatni, ale dokładna ocena częstości LE i CLE powoduje, że trial staje się negatywny. Ostatecznie ogólny zysk terapeutyczny niekonwencjonalnej radioterapii jest mierny, w granicach 0-15%. Analiza Znormalizowanych Dawek Całkowitych, skorygowanych dla zmiennej wartości dawki frakcyjnej i całkowitego czasu leczenia i szacowanych dla 50% prawdopodobieństwa LRC (NTCD5o) wskazuje, że przyjęta średnia dawka 0,6 Gy/dzień, równoważąca skutek repopulacji nowotworowych komórek klonogennych. może być zbyt niska i jej rzeczywista wartość średnia wzrasta do 0,85 Gy/dz., a nawet 1,1-1,2 Gy/dz. w czasie weekendów. Ponadto wydaje się, że okres spoczynkowy, poprzedzający repopulację, może być skrócony do 14-21 dni. Wnioski. Wyniki przekonywująco wskazują, że ograniczony zysk terapeutyczny może być wynikiem limitowania dawek całkowitych do poziomu tolerancji ostrego odczynu popromiennego, którego jednak nie można uznać za czynnik ograniczający wysokość dawki promieniowania. Stosowanie intensywnych schematów frakcjonowania, z użyciem dwóch dziennych dawek frakcyjnych, z nieznaczną redukcją dawki całkowitej lub jej brakiem, można jedynie rozważać w przypadku eskalacji dawki poza okres dni roboczych, tzn. z objęciem weekendów. Wyniki triali DAHANCA-7 i CAIR przemawiają za słusznością tej koncepcji. Jednakże, dla tak intensywnego leczenia, przedział bezpieczeństwa jest wąski i niewielkie zmiany całkowitego czasu leczenia lub dawki mogą powodować, że wzmożony ostry odczyn może ulec niebezpiecznemu nasileniu, wywołując następczy odczyn późny, przekraczający granicę tolerancji.
Pomimo dwóch dziesięcioleci szeroko zakrojonych badań nadal pozostaje otwartym pytanie, jakie są najbardziej skuteczne systemy frakcjonowanego napromieniania dla poszczególnych lokalizacji i stopni zaawansowania raków regionu głowy i szyi.

Key words: altered fractionation, head and neck cancer, therapeutic gain, consequential and late effects
Słowa kluczowe: zmienne frakcjonowanie, raki regionu głowy i szyi, zysk terapeutyczny, następcze i późne odczyny popromienne

Introduction

In conventionally fractionated radiotherapy for head and neck cancers late radiation effects in normal tissues were considered as the main threat to the quality of life and survival and the major factor to decrease therapeutic gain. Combination of RT 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 trials, application of more than one fraction per day of less than 2 Gy (hyperfractionation) produces increased sparing effects in late responding normal tissues at the expence of an increased incidence and severity of acute mucosal reactions. Shortening of overall treatment time (OTT) by acceleration the treatment may likely increase the risk and severity of both acute and late morbidity, especially if interfraction intervals are not long enough [1-5].

Biological rationale for improving treatment outcome by altered fractionation stemmed from the recognition of accelerated tumour clonogen repopulation as an obstacle to cure head and neck cancer. Mucosa epithelium also demonstrates this phenomenon, however it appears to start somewhat sooner and to proceed faster than in epithelial tumours. Exploiting differences in tumour and normal tissues repopulation leads to alteration of fractionation parameters to design accelerated (AF), hyperfractionated (HF) or hybrid (AHF) regimens. Integration of laboratory studies with bed-site observations was, and still is, the main objective of many clinical trials in order to increase therapeutic benefit, mainly for advanced head and neck cancers. Usually, treatment benefit is considered as an improvement of long-term local tumour or locoregional control. However, the assessment of benefit of altered radiotherapy should properly include both cost-benefit and cost-expense analysis.

Whilst cost-expense analysis needs formal and specific economical studies and the results may differ from center to center, and from country to country, the benefit is measured by the increase in locoregional control (LRC) or disease-free survival (DFS) and weighted against the costs. In this form of analysis, the costs mean dose-limiting normal tissue effects, which lower the LRC benefit to the level-free of complications. This is defined as a therapeutic gain, that is an increase in the rate of uncomplicated cures. However, the main problem arises which effects should be accounted for as limiting the efficacy of dose escalation and the tolerance. The majority of clinical trials on altered radiotherapy show an increased incidence and greater severity of acute mucosal reactions. Thus, it has been claimed that acute morbidity should be considered as the main dose-limiting factor, yet this appears to be based on belief rather than clinical evidence. Acute confluent mucositis is a frequent complication during RT but it is usually manageable and

certainly not beyond the limit of tolerance as the price for cure [3]. Above all, it is transient. Therefore, the clinically relevant criterium of acute tolerance should likely be determined by consequential late effects (CLE) which have to be avoided, if possible. Necrosis and consecutive fibrosis are clearly beyond the limit of tolerance because they are difficult to manage therapeutically and may lead to permanent morbidity [1]. For these reasons, both rates of the LE and the CLE have been chosen as the costs of altered RT and weighted against the LRC or DFS benefit to establish overall therapeutic gain.

Material and methods

Clinical data

For the present analysis the data sets of 12 clinical trials most often cited in the literature, including all together 4682 cases of head and neck cancer, have been selected. They represent all sites and stages of head and neck cancer and wide variety of altered dose-fractionation schedules, i.e. accelerated (AF), hyperfractionated (HF) of hybrid accelerated – hyperfractionated (AHF), given as a continuous, split-course, concomitant boost or escalated radiation treatment [6-18]. There are 9 trials on 5-days/week treatment, one trial on 6-days/week and 2 trials on 7-days/week treatment. In control arm (c) conventional fractionation with 1.8 Gy or 2.0 Gy per fraction, once-a-day (qd) was used, except PMH Toronto and RTOG 8809 trials where accelerated-like 51 Gy in 28 days or concomitant boost of 70.5 Gy in 42 days respectively, were used as a control regimens.

Dose Normalization

Because of large variation in total dose (D_i), dose per fraction (d_i) and overall treatment time (OTT), total dose was normalized to that (NTD) which would have been isoeffective if given in 2 Gy fractions, using formula [5]:

$$NTD = D_i [(\alpha/\beta + d_i) / (\alpha/\beta + 2.0)],$$

where α/β ratio of 15.0 Gy was used.
If there was difference in the OTT between two arms of a given trial the NTD was additionally corrected for repopulation using D_{rep} of 0.6 Gy/day [5].

To check the importance of the assumed α/β ratio to the conclusions drawn, alternative series of calculations were made using an α/β values between 10 Gy and 15 Gy, which are within the range commonly used in many studies. It was found that relative to a value of 15 Gy, an α/β ratio of 10 Gy only slightly increases the adjustment made to the total dose.

From the NTD values for altered (exp) and conventional (c) arm the difference (ΔNTD) was calculated as follows:

$$\Delta NTD = NTD_{exp} - NTD_c$$

and it was related to the LRC benefit (at least-3 year locoregional control).

Calculating TCD_{50} values

To intercompare LRC rates which usually differed from 50%, TCD_{50} values were calculated based on assumptions regarding cell killing in which the slope of the dose response curve reflects an effective D_o of 5 Gy. Change in dose to achieve 50% cure (P_{cure} 0.5) was calculated from:

$$NTCD_{50} = NTD_x + n \bullet {}_{eff}D_o$$
where $n = Ln (Ln\ 0.5/Ln_x)$

The value of 5 Gy for ${}_{eff}D_o$ rather than a lower value was chosen on the assumption that there would be heterogeneity of tumour and treatment characteristics affecting the slope of tumour control probability curves.

$NCTD_{50}$ values were plotted as a function of overall treatment time (OTT) and isoeffective dose-time curve was estimated.

Benefit end-points

Locoregional control rate (at least 3-years) was either clearly documented or it has been subtracted from the respective LRC curves, and they were used to calculate LRC benefit.

Costs end-points

For the present analysis, confluent mucositis (CM) is defined as severe mucosal reaction, and it corresponds with grade 4 of the EORTC scale or with Dische score >13. Increase in the incidence of the CM was calculated as a difference in the CM between experimental and control arm. Overall costs of altered regimes was estimated as a relative increase or decrease in the LE rates (including the CLE incidence) for experimental arm as compared with control, using formula:

$$COSTS\ (\Delta LE) = LE_{exp} - LE_{conv}$$

Therapeutic gain

Therapeutic gain (TG) means an improvement in uncomplicated locoregional control (≥3 yrs.) and it was calculated from:

$$TG = TG_{exp} - TG_{conv},$$
$$= LRC_{exp} \bullet (1 - LE_{exp}) - LRC_{conv} \bullet (1 - LE_{conv}),$$

Relative TG is given as a ratio of TG_{exp}/TG_{conv}

Incidence of severe late effects (severe fibrosis, necrosis or bone fracture, required surgical intervention and/or threatening quality of life) were documented as absolute numbers, rates or it was subtracted from the published curves of accumulated risk of LE or of late effect-free survival. However, the accuracy of the rate of LE considered as tolerance-limiting is uncertain to some extent because in some papers grade 3 effects were counted together with grade 2, and some figures are not interpretable as such, since several late events may occur in the same patient. Thus, in some situations overall costs might likely be under- or overestimated.

Consequential late effects (CLE) are morphologically-like typical late sequelae, and they can be recognized if developed early (≤6 months) after completing the treatment, and secondarily after the initial very severe confluent mucositis (grade 4, EORTC). If the CM healed after completing the treatment there is a short latency period to the onset of CLE, or if it is not, acute CM directly progresses into the CLE. For the present analysis the CLE clearly documented were included, and also those which characteristics of acute effects, the nature, and the onset likely allow to suspect they are consequential.

Results

Benefits vs. costs

The results of 12 clinical trials are listed in Table I.

Cairo trial (Tab. I-a): At the first glance AHF postoperative regimen gives 15% gain in the LRC as com-

Tab. I. Benefits and costs of the selected altered radiotherapy for head and neck cancer

No	Schedule and fractionation Dose / fractions / days		No. pts.	$\Delta NTD^{(xx)}_{2.0}$ Gy	TI (hours)	Benefit LRC	CM	Costs CLE	LE	Therapeutic gain	Author
	5 days/wk.										
(a)	AHF (t.i.d.)	42Gy/30fr./11d.	56	4.9 Gy	4	↑ 15%	↑ 25%	?	↓ 23%	14.5%	Awwad (6)
	Cairo	(c) 50Gy/25fr./35d.			*	(54% vs.39%)			(64% vs.87%)	(19.5 vs.5%)	
(b)	AF (b.i.d.)	66Gy/33fr./25d.	82	12.0 Gy	6	↑ 14%	↑ 46%	5%	↑ 15%	3.2%	Jackson et al. (15)
	Vancouver	(c) 66Gy/33fr./45d.			*	(70% vs.56%)					
(c)	AHF (b.i.d.)	58Gy/40fr./28d..	331	3.5 Gy	6	↑ 9%	↑ 14%	-	↓ 6%	10.4%	Cummings (9)
	PMH	(c) 51Gy/20fr./28d			*	(48% vs.39%)					
(d)	AH-S (t.i.d.)	72Gy/45fr./35d.	512	8.7 Gy	4	↑ 13%	↑ 36%	13%	↑ 10%	6.5%	Horiot et al.(14)
	EORTC 22851	(c) 70Gy/35fr./49d.			*	(59% vs.46%)			(for LEFS ↑ 21%)	- 2%	
(e)	AH-CB (b.i.d.)	72Gy/42fr./42d.	79	5.4 Gy	6	↑ 13%	↑ 18%	-	no diff.	13%	Ang et al. (7)
		arm III-last $2^1/_2$ wk.			6	(79% vs.66%)					
		(c) arm I +II – first $2^1/_2$ wk. + twice-a-week									
(f)	AH-S (b.i.d.)										
	vs. CB	67.2Gy/42fr./42d.	70	(4.9 Gy	6	↑ 16%	↑ 7%	-	↑ 11%	15.5%	Fu et al. (12)
	RTOG 8809	70.5Gy/41fr./42d.			*	(47% vs.31%					
(g)	HF (b.i.d.)	80.5Gy/70fr./49d.	320	6.5 Gy	4 – 6	↑ 19%	↑ 18%	-	↑ 2.9%	16.2%	Horiot et al. (13)
	EORTC 22791	(c) 70Gy/35fr./49d.				(59% vs.40%)					
(h)	HF-AHF (b.i.d)	HF 81.6 Gy/68 fr./48 d.	1073	7.7 Gy	6	7.6%	↑ 20%	-	↑ 5%	4.4%	Ang, Fu (8)
	RTOG 9003					(53.7% vs.46.1%)					
		AHF-S 67.2Gy/42fr./42d.		no diff.	6	1.6%	↑ 16%	-	↑ 3%	NO (0.06%)	
						(47.7% vs.46.1%)					
		AHF-CB 72.0Gy/42fr./42d.		6.6 Gy	6	8.1%	↑ 24%	-	↑ 3%	5.9%	
		(c) 70.0Gy/30fr./48d.				(54.2% vs.46.1%)					
				-	*	-	-	-	-	-	
(i)	AHF (b.i.d.)	AHF 59.4Gy/35fr./24d.	350		6	3%			↓	3%	Denham (10)
	TROG 9101	(c) 70.0Gy/35fr./47d.		2.5 Gy	*	(54% vs.51%)	↑ 30%	-	no diff.		
	6 days/wk.										
(k)	AF (q.d.)	66Gy/33fr./39d.	791	4.2 Gy	24	↑ 9%	↑ 20%	-	no diff.	9%	Overgaard et al.(17)
	DAHANCA 7/5	(c) 66Gy/33fr./46d.			*	(66% vs.57%)					
						[(12% for T situ]					
	7 days/wk.										
(l)	AHF(t.i.d.)	54Gy/36fr./12d.	918	2.4 Gy	6	5%	↑ 30%	-	↓ 4%	6.5%	Dische et al. (11)
	CHART	(c) 66Gy/33fr./45d.			*	(45% vs.40%)					
(m)	AF (q.d.)	70Gy/35fr./35d.	100	14.0 Gy	24	45%	↑ 36%	11%	↑ 6%	36.5%	Składowski et al.(18)
	CAIR	(c) 70Gy/35fr./49d.		(8.4)	*	(82% vs.37%)					

[AF- accelerated; AHF – accelerated/hyperfractionated; HF – hyperfractionated; s – split; CB – concomitant boost; q.d. – once-a-day; b.i.d. – twice-a-day; t.i.d. – trice-a-day; c – control group; * – conventional 24^h interfraction interval; ** – see footnote in the text]

pared with conventional control. When the LE costs are accounted for an overall therapeutic gain (TG) is still close to 15%, suggesting that the AHF might relatively be even 3.9 times more effective than conventional regimen, (19.5% / 5%). However, unacceptably high rates of the LE make the TG rate in both arms far below the initial LRC level in the control arm. Moreover, there were two times more patients with adequate surgical margins in control group. If one would agree that it is a crucial prognostic factor for treatment outcome, specific analysis may likely suggest no gain at all for this trial.

Vancouver trial (Tab. I-b): Overall treatment time (OTT) is the only variable in this trial, and shortening the OTT by 20 days gives 1.2% benefit in the LRC for each 1 Gy increase in effective $NTD_{2.0}$, suggesting fairly shallow dose response curve ($\gamma = 0.78$) probably due to heterogeneity of tumour sites and stages. The LRC benefit is, however, neutralized by 15% higher costs (late toxicity) in the AF arm, and thus overall therapeutic gain decreases to only 3.2%, and suggests no advantage of the AF schedule. The trial was discontinued after randomisation of 82 pts.

PMH vs. CHART (Tab. I-c,l): The PMH with fractionation given b.i.d. in 4 weeks (5 days/week) and the CHART with t.i.d. in 12 days (7 days/week) with essentially the same dose per fraction (1.45-1.5 Gy) are compared. In both trials the LE costs in the altered arm were lower than in the control, and thus therapeutic gains (TG) were slightly higher than LRC benefits. For both trials, each 1 Gy increase in the NTD_2 produces 1.7-1.9% improvement in the TG. It is however, intriguing that the CHART showed higher benefit for advanced laryngeal tumours, and no advantage for T_{1-2} and for oral cavity, oropharynx and hypopharynx, whereas the PMH produced significant LRC benefit of 12% for small tumours (<4 cm), and no gain for larger ones (>4 cm). Furthermore, the best improvement for hypopharyngeal tumours was noted although present in all sites. The results of both trials suggest that a large reduction of the total dose, to circumvent mucosal reaction, associated with drastic shortening of treatment time might neutralize the potential benefit of accelerated schedules.

EORTC 22851 (Tab. I-d): This trial explored the t.i.d. accelerated hyperfractionation with shortening the OTT by 24 days, and total dose similar to that in conventional arm. The difference in effective $NTD_{2.0}$ was 8.7 Gy producing 13% LRC benefit. For unfavourable T & N patterns (any T, N_{2-3}, T_4 any N) LRC benefit in favour of the AHF-S arm was even higher (18%), however with no advantage for nodes, survival and specific survival. Oral cavity and oropharyngeal tumours did significantly worse.

Evaluation of the costs leads to confusing interpretation. Overall incidence of the LE of 10% higher in the AHF-S arm corresponds with the decrease in therapeutic gain to 6.5%. However, when late-effect free survival is accounted for the difference of 21% in disfavour of AHF-S gives no gain at all (-2%). Although consequential late effects are not directly defined and counted, it looks that 13% of severe protracted grade 3 mucosal sequelae might likely be considered as the CLE. Therefore, both costs and therapeutic gain are uncertain because the incidence and severity of late effects (grade 2 and 3 are groupped together) are not interpretable as such, since several events may occur in the same patient. Although, the AHF-S might be beneficial for some advanced tumours, such intensive t.i.d. schedule with insufficient 4-h interfraction intervals appears to be too toxic.

RTOG 8809, MDACC-CB, RTOG 9003 (Tab. I – e,f,h): Comparison of these three the US trials is quite surprising. The RTOG 8809 trial published in 1995 was designed to establish the patient tolerance to each of the two (split-course vs. concomitant boost) altered regimens rather than to test for differences between them. However, it showed, although not significant, but still substantial 16% LRC benefit in favour of the AH-S arm referred to the $\Delta NTD_{2.0}$ of 4.9 Gy. Perhaps due to the same dose per fraction in two arms no significant increase and difference in late toxicity has been noted, and permanent grade 4 late toxicity was 6% for the split and 7% for the concomitant boost.

A few year earlier the MDACC tested efficacy of the concomitant boost (CB) in the three-arm trial. It showed 13% LRC benefit in favour of the CB given during the last $2\text{-}2^1/_2$ wks as compared with the CB given either twice a week during the basic course or during the first $2\text{-}2^1/_2$ wks There was no difference in costs between three arms, with only a slightly higher (18%) incidence and severity of acute mucosal reactions when the boost has been given during the first $2\text{-}2^1/_2$ wks. However, what is surprising is that the LRC rate of 79% was about 2.5 times higher than in the CB arm of the RTOG 8809 although in both trials almost the same tumour sites and stages were included.

Recently reported RTOG 9003 trial has compared three different altered regimens with conventional fractionation. It showed 7- 8% LRC benefit in favour of hyperfractionation (HF) and concomitant boost (CB) with no advantage of the split-course (S). Because the costs (LE) were slightly higher in altered arms, overall therapeutic gain decreased to 4.4% and 5.9% for the HF and CB respectively, and almost to zero (0.07%!) for the S. No advantage for the split-course is not surprising because the effective $NTD_{2.0}$ was almost the same as in the control. In fact, the LRC rates for the split-course regimen in the RTOG 8809 and RTOG 9003 were exactly the same. What is, however, confusing and difficult to explain, is why $NTD_{2.0}$ in the RTOG 9003 higher than in the MDACC produced 1.5 times lower LRC benefit and therapeutic gain. It is also difficult to understand why in the RTOG 8809 the LRC benefit in favour of the split regimen has been achieved by the NTD dose of about 5 Gy lower than that for the CB. It seems that even tumour heterogeneity and selection bias might unlikely explain these opposed results and conclusions.

EORTC 22791 (Tab. I-g): In contrast to other trials this one includes fairly homogenous group of $T_{2-3}N_{0-1}$ oropharyngeal cancers. For the first time, the results have shown convincing advantage of hyperfrac-

tionation with overall LRC benefit of 19% as the result of increase in the $NTD_{2.0}$ of 6.5 Gy. For T_3 tumours LRC benefit was even of 35%, but not for T_2 tumours and all nodes. Once again, it is difficult to quantify the costs since late effects (grade 2 and 3) were groupped together and several events may occur in he same patients. Nevertheless, overall difference in the LE rates between two arms was of 2.9% (8.8% vs. 5.9%) resulting in therapeutic gain of 16%. This TG was about 3.5 higher than the respective gain for the HF arm in the RTOG 9003 trial. It is difficult to answer whether it simply reflects more advanced tumours in the RTOG than in the EORTC trial.

TROG 9001: The Trans-Tasman trial used the AHF regimen of 1.8 Gy fractions given b.i.d. in the OTT shortened by 23 days. Total dose was only slightly reduced to 59.4 Gy and it is almost equivalent to conventional 70 Gy in 35 fractions in 47 days. The LRC rate in both arms was almost identical and close to 50% (3% LRC benefit in favour of the AHF). The most important point to emerge from the results is that by shortening the OTT by about 3 weeks a total dose of 59.4 Gy given b.i.d. is isoeffective to 70 Gy in 7 weeks, and they both can be interpreted as TCD_{50}. For the first time, acute and late effect as the costs of this trial were precisely quantified [1], and the results showed that although the acute CM was more frequent (30%) in AHF arm they have been quite well tolerated by patients. The important observation is the duration of CM was inversely related to the time to onset of the reaction. For both arms similar hazard ratio for grade 3 late effect was at the range of 1.20-1.22. Acute and late effects were observed more commonly in patients with oral cavity and oropharyngeal tumours.

DAHANCA-7 and CAIR (Tab I.-k,m): These two trials tested the concept that simple continuous course using 2 Gy daily fractions, 6 or 7 days, instead of 5 days a week, may likely to offer at least the same benefit with less late effects.

The DH-7 trial showed a significant 9% LRC benefit for 6 days/week regimen independent on tumour site and stage, however, with no advantage for nodes. For T-site only the LRC benefit was of 12%. Analysing the costs an increase (20%) in acute (all were reversible and healed within 2 months after RT) but not in late toxicity has been observed. Thus, giving 6 days/week treatment with moderate shortening of the OTT by one-week resulted in a significant therapeutic gain of 9-12%. Furthermore, well and moderate differentiated tumours appeared to gain more from accelerated regimen then undifferentiated tumours (27% vs. 10% in gain the LRC). The issue related to tumour differentiation is intriguing and becomes one of the important target for future studies. The 6 days/week regimen has become standard radiotherapy for head and neck cancer in Denmark.

The CAIR made one step further by giving 7 fractions in 7 days and shortening the OTT by 2 weeks. It resulted in the LRC benefit of 45%. Although such unexpectedly high benefit might be uncertain and questionable, it has to be pointed out that the benefit is related only to homogenous group of $T_{3\text{-}4}N_{0\text{-}1}$ oral cavity and oropharyngeal tumours. In contrast to DH-7, in the AF arm of the CAIR, when 2 Gy fractions were used, 22% of consequential late effects have developed relatively early during follow-up. For that fraction size therapeutic gain decreases to only 30%. However, when dose per fraction was lowered to 1.8 Gy no more CLE occurred, and overall late effects (including CLE) were only 6% higher than in control arm. Finally, therapeutic gain of 7 days/week regimen is 36.5%. Despite the risk of CLE, acute reactions, although more frequent in 7 days/week arm, have not been dose-limiting, but tolerable by patients. Therefore, 7 days/week regimen became in Gliwice a standard treatment for $T_{3\text{-}4}N_{0\text{-}1}$ oral cavity and oropharyngeal tumours.

Discussion

This review of the most often cited trials on unconventional fractionation likely suggests that altered regimens are probably not universal „golden key" for radiotherapy for advanced head and neck cancer, and still it can rather be considered as a „Holly Grail" because too many questions remain unanwsered.

LRC benefit

Although there is general trend of the LRC benefit in favour of different combinations of accelerated and/or hyperfractionated regimens, the detailed analyses lead to considerable confusions. In some studies the AF/AHF regimens were superior for advanced tumours (CHART, EORTC 22791) but not for T_2, whereas in others significant benefit was noted for tumours smaller than 4 cm (PMH). Despite the majority of trials cover all tumour sites and stages, the PMH trial has documented the best LRC benefit for hypopharyngeal tumours, whereas CHART in contrast, showed a significant improvement for $T_{3\text{-}4}$ laryngeal cancer with no advantage for oral cavity, oropharynx oral hypopharynx. There is substantial evidence of higher LRC benefit for specific subgroups of patients than overall improvement. The EORTC 22851 trial noted the LRC benefit for T_4 tumours about 6% higher than overall gain, marginal benefit for $T_{2\text{-}3}N_{0\text{-}1}$, and the worst prognosis for oral cavity and oropharynx. In DAHANCA-7, also 6% higher benefit was noted when T--site was accounted for the analysis. In the two trials it was noted [11,17], that well differentiated tumours responded better to accelerated regimens than poorly differentiated. This feature may closely be related to the normal cells from which the tumours have their origin. Thus, the ability of squamous epithelium to rapidly proliferate in response to radiation injury may be retained by well and moderate differentiated but lost in the poorly differentiated cancers.

Comparison of the three US trials reveals a few uncertainties. The RTOG 8809 showed the LRC advantage of the AH-split-course over concomitant boost (CB), whereas in the RTOG 9003 no gain at all was noted for the split-course altered regimen and the CB was found

the most effective, supporting earlier results of the MDACC trial. However, it is difficult to explain why the LRC benefit of the CB was about 1.5 times lower in the RTOG 9003 than in the MDACC although dose fractionation pattern was the same, and similar T-sites and stages have been recruited to both trials. Similar uncertainty arises comparing the HF arm of the RTOG 9003 with the EORTC 22791 which reported about 2.5 times higher LRC benefit than that noted in the US trial.

The next potentially surprising point to emerge is that overall or specific LRC benefit in all trials is related to an average (median) total dose and fractionation pattern, although in some trials a wide range of dose is used [14]. If a total dose is, for example, in the range of 70-76 Gy, and dosimetric error is of about 5% (this parameter is almost never reported in the published reports) it gives the dose range even wider, from 66.5 Gy to 79.8 Gy. Thus, such large scale of dose reflects a whole range of dose-response curve rather than a single LRC rate-dose point, which in fact, is a basic assumption, for a given trial. It seems likely that even within homogenous T-site and stage subgroups, patients receive different total doses and overall treatment times. Therefore, overall LRC benefit is only an average value reflecting unknown variations in LRC rates and in radiation doses. Moreover, the imbalance of case distribution into treatment arms concerning predictive parameters is crucial for validity of the interpretation of the results with regard to treatment outcome, and thus benefit of altered fractionation might be underestimate in some trials or overestimated in others.

Costs and therapeutic gain

Interpretation of the costs (acute and late morbidity) is even more uncertain than that of the LRC benefit. Obviously causion is necessary in interpreting acute mucosal reactions, but although an increase in the incidence and severity of acute mucositis (CM) was usually noted for altered regimens, the most severe reactions have been transit and usually subsided within 2-3 months after completing the treatment (Fig. 1). Thus, they do not seem to be dose-limiting. What important is pointed out by Denham et al. [1] is that duration of the CM is inversely related to the time to onset of the reaction, that means, the longer acute CM lasts (>20 days) the earlier it develops. The authors also noted that duration of the CM might be a good quantitative surrogate for the level of acute mucosal cellular depletion caused by a fractionation regimen.

There is a good clinical evidence that late mucosal reactions occur in part as a consequence of acute denudation of squamous epithelium [1]. The TROG 9101 and CAIR data show that the acute CM lasted longer than 3 weeks strongly correlates with the risk of consequential late effects (CLE). This raises concern that late normal tissue sparing from hyperfractionated regimens may be off-set by increased risk of the CLE. According to Denham et al. [1] the hazard ratio for grade 3 late reactions in the TROG 9101 was 1.2 for each increasing week spent at the CM level. Nguyen and Peracchia studies [19, 21] on highly intensive short accelerated regimens support this suggestion. Also escalated accelerated regimens tested in phase I studies by Kaanders et al. [16] and Harari et al. [2] produced unacceptable incidence of the CLE. All these regimens have been abandoned, and never entered into phase III trials.

There is convincing evidence that both consequential (CLE) and typical late (LE) normal tissue reactions should be considered as a true dose-limiting events (costs) of altered radiotherapy (Fig. 1, black area within the graphics symbolizes CLE). Although it is difficult to separate CLE from LE and they both might be very heterogeneous in their nature and in morphologic patterns, and difficult to quantify, the tools used in clinical trials to quantify late effects have not generally been validated. Thus, many inconsistencies arise from inconclusive collection and reporting of late effects. They are usually reported as a composite of grade 2 and 3, whereas only the grade 3 reactions can be regarded as dose-limiting. In the EORTC 22791 no separate information was given about the relevant endpoint for late reactions. In the EORTC 22851 the CLE of 13% can only be deduced indirectly from signs and duration of the acute effects.

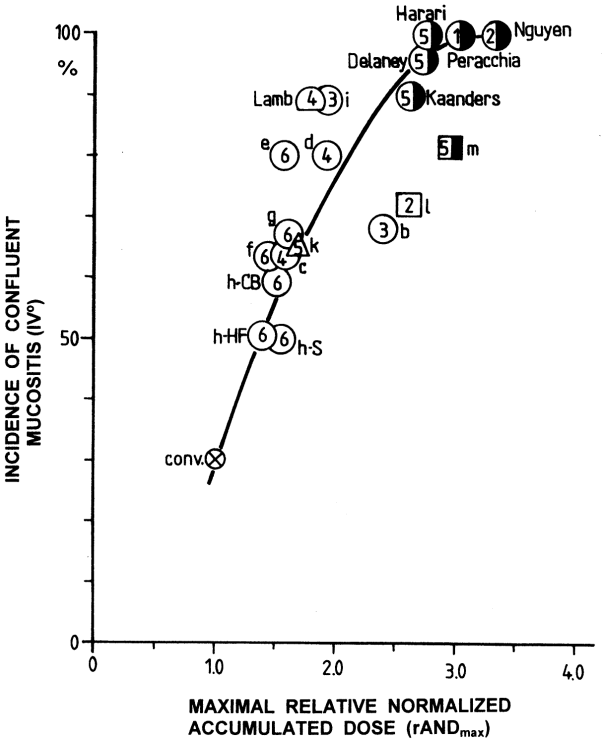

Fig. 1. Incidence of acute confluent mucositis (CM, IV°) against maximal Relative Accumulated Normalized Dose per week (rAND$_{max}$).
Number in graphics gives a week in which rAND$_{max}$ reaches the highest value. The rAND$_{max}$ was normalized to 2.0 Gy fraction regimen using α/β of 15.0 Gy and corrected for normal mucosal repopulation using on average of 1.0 Gy/day and the lag period of 14 days. Relative AND$_{max}$ was calculated as a ratio of maximal value of AND for altered regimen and conventional AND for the respective week of treatment. Conventional AND$_1$,AND$_2$, AND$_3$,... AND$_6$ equal 10 Gy, 20 Gy, 23 Gy,... 29 Gy. Five additional data sets are included to show the risk of consequential late effects (black area within the graphics): [fractionation: half-circle – 3 days/wk., circle – 5 days/wk., triangle – 6 days/wk., square – 7 days/wk.]

In contrast to tumour response most often reported as an actuarial analysis, late reactions are mainly given as a crude data yielding underestimation of complication incidence. The increase in total dose from 70.0 Gy to 80.5 Gy (in fact, it is only 6.5 Gy increase in effective $NTD_{2.0}$) leads in the EORTC 22791 trial to the increase in the LRC for T_{3-4}, but not for T_2. However, the benefit for T_3 tumours might partially be compensated for, because grade 3 late effects probably increased simultaneously. On the other hand, the benefit for T_2 tumours can not be ruled out, since normal tissue data were not broken down by tumour stage. Thus, therapeutic gain as the result of the LRC benefit weighted against the costs remains uncertain, and it is clearly illustrated by the results of the EORTC 22851 trial. If the reported 10% increase in overall rate of late effects is weighted against LRC benefit of 13% therapeutic gain is of 6.5%, whilst the late effect – free survival is accounted for as an end-point, therapeutic gain becomes negative.

The results of Cairo trial are also misleading (Tab. I). Almost no decrease in therapeutic gain (14.5%) is noted when the LRC benefit is weighted against the costs, but in fact, the TG in both arms is far below the control LRC suggesting the trial might also be considered as „negative".

Finally, analysis of acute and late effects in the TROG 9101 trial show that in contrast to severe mucosal reactions being site-independent, late effects developed less frequently in hypopharynx and larynx than in oral cavity and oropharynx. Thus, tumour site heterogeneity, mainly in the multicenter trials, and its imbalance in favour of one arm may additionally be the cause of over- or underestimation of the therapeutic gain, independently on dose escalation.

Among the reviewed trials, the CAIR shows the highest LRC benefit in favour of 7 days/week regimen, and even if late effects are accounted for an overall therapeutic gain remains unexpectedly high. Although it might be true such results should carefully and critically be interpreted because if a trial is small and it reaches significance, then the observed difference might likely be overestimated.

Importance of overall treatment time (OTT)

The results of all trials clearly confirm the radiobiological concept that overall treatment time reflecting accelerated tumour clonogen repopulation is a major determinant of the LRC benefit in radiotherapy for advanced head and neck cancer. Although it seems obvious, therapeutic gain associated with OTT contraction can only be guessed indirectly because of variation in fractionation parameters. Figure 2 shows an increase in the therapeutic gain (TG) with shortening of the OTT. This comparison shows that no single value of the TG per one day shortening of the OTT can be calculated. CAIR and DAHANCA-7 trials where change in the OTT was the only variable imply 1.5-2.5% increase in the TG per each one day contraction

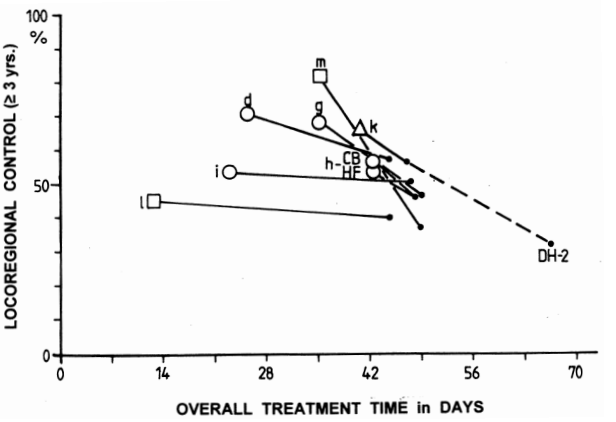

Fig. 2. Therapeutic gain (LRC benefit – late effect costs) against overall treatment time. Only trials with difference in OTT between arms are included.
[black point represents control group; graphics and letter symbols as in Tab. I]

of the OTT in the range from 7 to 5 weeks. However, when the OTT was dramatically shortened from 6-7 weeks to 2-3 weeks, the increase in TG related to change in the OTT becomes very small, i.e. 0.1-0.4% / 1 day contraction. It can be the result of too large reduction of the total dose to circumvent mucosal reaction associated with drastic reduction of treatment time, which may neutralize the potential benefit of treatment acceleration.

Accelerated arms in the EORTC 22851 trial and in the CAIR differ by the only fact that the former is „weekend free" and the latter is „weekend busy" treatment. Difference in the TG for altered arms of both trials is 19.8% (70.5% vs. 50.7%). Assuming that tumour repopulation begins around day 21 this difference gives about 5% increase in the TG per each one day of the weekend. Because such high increment in the TG seems unrealistic, another explanation might be that accelerated repopulation begins earlier, that means around day 14. It would give an increase in the TG of 3.3% / 1"weekend day". Thus, the suggestion there is no reason to shorten overall treatment time to less than 4 weeks does not seem plausible.

Although all the above speculations might be more or less acceptable, it seems the OTT might not be the only important and independent factor influencing therapeutic gain. Despite the OTT contraction, it is also important how intensively daily dose (one, two or three daily fractions) is accumulated during the course of treatment, and how large is reduction of total dose. The TROG 9101 trial shows that for 4-week treatment total dose of about 60 Gy is almost equivalent to 70 Gy given in 7-weeks, and they both are close to the TCD_{50} values.

Importance of total dose

Comparison of LRC benefit for different altered regimens becomes useless and misleading if it is simply related to physical total dose because of wide variation in size of dose per fraction, number of daily fractions, and in overall treatment time. At the first glance, the same loco-

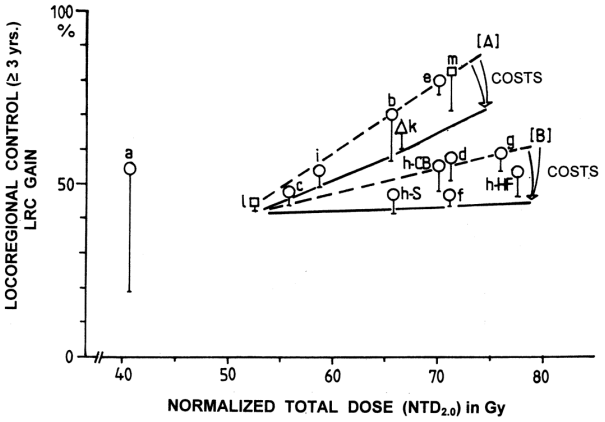

Fig. 3. Locoregional control against Normalized Total Dose ($NTD_{2.0}$) without correction for overall treatment time.
[vertical lines represent decrease of the LRC to therapeutic gain due to the incidence of late effects; solid lines represent the LRC – NTD, and dotted line the TG – NTD relationships; area between two curves illustrates the risk of costs-late effects. Graphic and letter symbols as in Fig. 1]

regional control rates of 47-48% for the PMH and the RTOG 8809 have apparently been produced by quite different doses of 58 Gy and 67.2 Gy. However, they become almost the same of about 56 Gy if corrected for change in dose per fraction and in overall treatment time, assuming the onset of accelerated repopulation on day 28. In the TROG trial physical dose of 70 Gy in 47 days is higher than 59.4 Gy in 24 days, however they both are biologically isoeffective producing almost the same LRC rate of 51% and 54%. In contrast, in the DAHANCA-7 trial the same physical total doses of 66 Gy in both arms produced different LRC rates of 66% and 57%, since they differed biologically by at least 4.2 Gy.

All the above examples explain why physical total dose should be converted into Normalized Total Dose ($NTD_{2.0}$) if the treatment efficacy is compared. Scattergram of the LRC benefits and costs plotted as a function of the $NTD_{2.0}$ (Fig. 3) shows that there is no single and simple relationship between the TG and the $NTD_{2.0}$, and at least two subsets of the LRC costs-dose relationship can be seen.

The upper panel A collects the trials with high or increased total dose and with pronounced shortening of overall treatment time, that means, very intensive regimens. For this subset an average increase of LRC benefit is of the about 2.3-2.5% per each 1 Gy increment in the $NTD_{2.0}$. The costs lower therapeutic gain to 1.25% / 1 Gy increment in the $NTD_{2.0}$. The lower panel B represents less intensive altered regimens, without or with slight reduction in overall treatment time and it shows much smaller increase in the LRC benefit of about 0.55% / 1 Gy increase in the NTD, and almost no therapeutic gain.

The important point to emerge from this analysis is that both LRC benefit and overall therapeutic gain significantly depend on dose intensity delivered in a given time. The longer OTT is used (less contraction) the more intensive dose fractionation should be used. Any compromise in dose reduction due to pronounced shortening of the OTT usually dilutes the expected therapeutic gain. The CHART results support this relationship.

The second important conclusion would be that any treatment end-point should not be considered in terms of dose intensity separately from of overall treatment time, because the power of these two parameters is closely interdependent. Additionally, Figure 3 shows a tendency of almost the same „cost-area" (area between solid and dotted line) for two subsets of data independent on changes in dose and in time. It suggests that the size of therapeutic gain might seriously be constrained by the false intention to limit total doses to the level that do not exceed acute mucosal tolerance which seems to be a myth rather than proved by clinical evidence. On the other hand, because our knowledge on consequential and late effects remain unprecise and fragmentarical true dose-limiting level is still uncertain.

Therapeutic gain vs. increase in effective NTD

Assuming that, in altered fractionation change in dose and in time depend on each other and they should be counted together, the LRC benefit and therapeutic gain for various trials is weighted against an increase in the NTD* (corrected for the OTT) for experimental arm as compared with control (Fig. 4). It shows an average increase in the LRC benefit of about 3% per each 1 Gy increment in the effective NTD2.0 and slightly less (about 2.5%) in therapeutic gain. For very short regimens the costs of altered schedules appear to be even lower than for conventional standard.

It is interesting to note that on Figure 4 four data points are far below the estimated curve. In two trials (EORTC 22851 and Vancouver) unexpectedly high risk of CLE and LE significantly neutralized the LRC benefit. However, it is hard to explain such low gain in two arms of the RTOG 9003 (CB and HF) especially if compared with the EORTC 22791 and MDACC trials.

Figure 4 generally implies that even if the doubts concerning accuracy in the scoring and recording of consequential and late effect would be accounted for there still would be a room to increase dose intensity in order to improve therapeutic gain.

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* *Footnote*: Assuming 60 Gy in 30 fractions is a standard regimen, and the tested altered regimen (A) would be given in 1.6 Gy fractions b.i.d. to a total dose of 62.4 Gy, one could say there is 2.4 Gy increment in effective total dose (assuming overall treatment time is the same in both regimens). However, it is not true, because there is no increment in effective dose at all, and 62.4 Gy in regimen A is just equivalent to standard 60 Gy (assuming α/β value of 15.0 Gy). If the increase in effective dose would be 2.0 Gy, which is equivalent to 2.1 Gy in 1.6 Gy fractions, then total dose in regimen A should be 64.5 Gy giving therapeutic ratio of about 1.03 or 3% (64.5/62.4). On the other hand, 10% gain in effective dose (ratio = 1.1) would give total dose of 68.6 Gy and absolute increment in the effective normalized dose (ΔNTD) of 6.2 Gy (68.6 Gy – 62.4 Gy) instead of 8.6 Gy (68.6 Gy-60 Gy). This example shows the way in which $\Delta NTD_{2.0}$ is calculated, and should be interpreted.

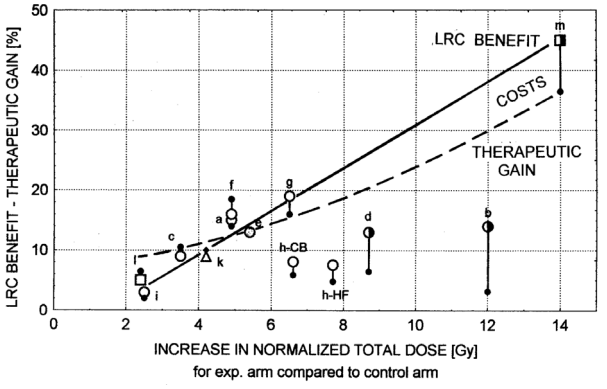

Fig. 4. LRC benefit (therapeutic gain) as a function of the increase NTD2.0 (with correction for overall treatment time) for the tested altered regimens as compared with control.
[solid line – LRC benefit; dotted line – therapeutic gain; area between lines – CLE and LE costs; graphics and letter symbols as in Fig. 1; black area within the graphics represents incidence of CLE; dose correction for difference in the OTT between two arms was calculated using 0.6 Gy/day and referred to the regimen with shorter OTT]

Is tumour repopulation a major determinant of therapeutic gain?

Majority of altered regimens, including those analysed in the present paper, were designed based on radiobiological rationale that reduction in dose per fraction given more often than one daily fraction produces sparing effect in late responding normal tissues, and that shortening of overall treatment time compensates accelerated tumour repopulation. Fundamental guidelines have been rised by Withers et al. [21, 5] suggesting that tumour clonogen repopulation compensates on average 0.6 Gy/day after a lag period of about 28 days (Fig. 4A – solid lines). Despite many uncertainties, the Withers' „dog leg" curve was explored for at least the last 12 years as a basic rationale for altered accelerated and/or hyperfractionated strategies although the rationale came from the analysis of a spectrum of predominantly retrospective studies. Moreover the length of the lag period can only be defined from accurate estimates of TCD_{50} for advanced head and neck cancers treated in short overall treatment time, however, in fact they were not available at the time of analysis.

During the last decade many results of clinical trials have been published, also those with the OTT of 28 days and shorter. Total doses for altered regimens in the trials reviewed in this paper are converted into $NTD_{2.0}$ and recalculated as $NTCD_{50}$ values, and they are plotted against overall treatment time in Figure 4A. This figure shows that at least ascending part of the original curve with the slope of 0.6 Gy/day is far below the analyzed data points. It suggest that the impact of accelerated repopulation on treatment outcome might be higher than originally suggested by Withers et al. [5], and more than 0.6 Gy/day might be compensated beyond day 28, and probably it is not constant with the extension of overall treatment time. In TROG 9101 and PMH trials, the $NTCD_{50}$ values of 58.1 Gy and 56.4 Gy respectively for the OTT of 24 and 28 days suggest that between day 24 – 28 accelerated repopulation is already ongoing. Assuming 0.6 Gy/day for that short range of the OTT the lag period could be shortened to 21 days. However, if it is true that well-differentiated epithelial cancer respond better to altered regimens (as observed in DH-7 and CHART) because they reflect the characteristics of normal epithelium from which the tumours have their origin, thus a lag period of even 14 days sounds also reasonable.

In 1990 Cox et al. [22] published the results of the RTOG 8313 trial testing efficacy of 4 different total doses given b.i.d., and they observed no difference in therapeutic gain for total doses in the range of 72.0 – 81.6 Gy. The respective $NTCD_{50}$ values are 69.8 Gy and 78.3 Gy. Assuming 0.6 Gy/day to balance the repopulation, from the difference in $NTCD_{50}$ of 8.5 Gy, only 3.6 Gy (6 days x 0.6 Gy/day) would be balanced by repopulation, and the remaining 4.9 Gy should reflect an increase in the therapeutic gain. However no gain was observed. It may likely suggest that all 8.5 Gy could be balanced by accelerated repopulation, and consequently dose compensated by repopulation per day would be 1.6 Gy instead 0.6 Gy/day, at least for the OTT of 6 weeks and longer.

A few recent trials, namely EORTC 22851, and RTOG 9003 (arm HF, CB and S), convincingly suggest that accelerated repopulation beyond day 28 of treatment counterbalances about 1.1-1.2 Gy/day rather then 0.6 Gy/day. Thus, curve (a) and (b) on Figure 4B might not be acceptable. The curve (c) gives the best fit to the data, however the curve (d) reflecting the lag period of 21 days and an average rate of repopulation of 0.85 Gy/day thereafter can not be neglected. It may suggest that higher power for repopulation should be given if therapeutic gain larger than 5-10% would be expected. For overall treatment time longer than 4-5 weeks about 7 Gy/week will be lost counterbalancing accelerated repopulation instead of only 4.2 Gy/week. Therefore, only a part of the increment in total dose, that above 7 Gy/week, may have an effective impact on therapeutic gain.

The next and potentially interesting point to emerge from Figure 4A is that $NTCD_{50}$ of 68.7 Gy and 63.8 Gy for the EORTC 22851 and CAIR trials differ only by the fact that in the first trial a total dose was given in 5 days and in the second one in 7 days per week. Therefore, by extending irradiation on weekends instead of 5 days a week allows to decrease isoeffective dose by 4.9 Gy. If the lag period of 28 days would be right, dose balancing tumour repopulation during weekends will be irrationally high of 2.45 Gy/day, but if a lag period would be 21 days it will give 1.2 Gy/day (4.9 Gy / 4 days – 2 weekends). The latter one sounds radiobiologically more realistic. Independently on assumption the estimates likely suggest that repopulation during the weekends could be more effective than during weekends.

Is LRC rate for control important for overall therapeutic gain?

Recently Hliniak has pointed out (personal communication) that nobody knows why the control LRC level which the LRC benefit is refered to is generally ignored. Let

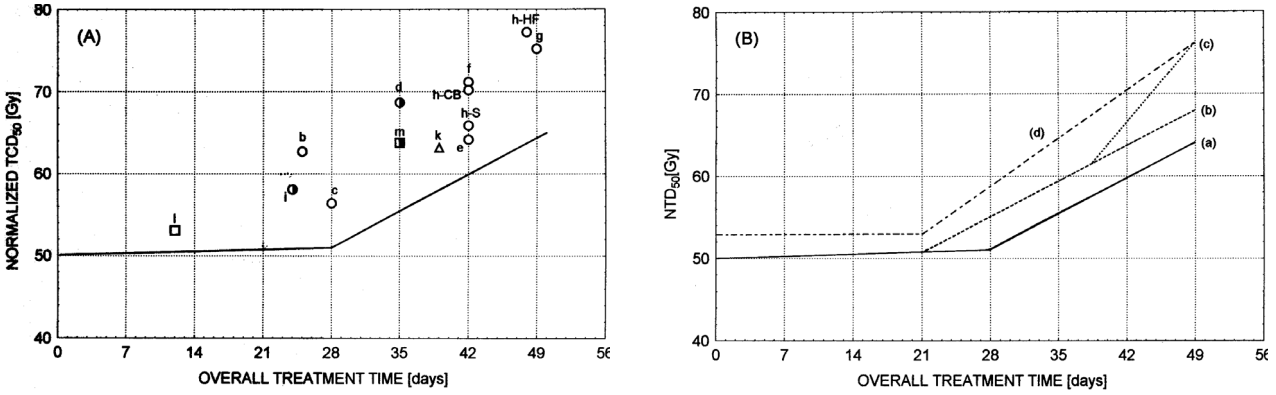

Fig. 5. $NTCD_{50}$ values as a function of overall treatment time for advanced head and neck cancers estimated from the reports (letter symbols represent authors and references), and normalized to 2.0 Gy fraction regimen. Constrains on data analysed were all H & N sites and stages included, LRC rate in the range of 47%-82% (it minimalize extrapolation errors in estimating $NTCD_{50}$), and α/β = 15.0 Gy. $NTCD_{50}$ – time curve is originally estimated by Withers et al. (24)
Original dose-time curve (a) estimated by Withers in 1988 with the average slope of 0.6 Gy/day after the lag period of 28 days compared with the curves which give a better fit to the analysed data:
(b) constant slope of 0.6 Gy/day with the lag period of 21 days;
(c) biphasic slope of 0.6 Gy/day between day 21 and 38, and 1.2 Gy/day thereafter, and with the lag perior of 21 days;
(d) constant slope of an average 0.85 Gy/day after the lag period of 21 days and with the TCD_{50} of 53 Gy in the absence of accelerated repopulation (until day 21)

us assume the same LRC benefit of 15% for two different trials. This may suggest that both trials are equally effective. However, it could not be true, since it would depend to what level of the control LRC this 15% benefit will be refered. If, for example, in one trial the control LRC is 35% then altered regimen with the LRC of 50% (15% benefit) will be 1.43 (43%) more beneficial than the control. In contrast, the same increment in the LRC but related to the control LRC of 55% will produce only 1.27 (27%) benefit.

According to that, the AH-S regimen in the RTOG 8809 is more beneficial (1.53) than HF regimen in the EORTC 22791 (1.43) although the absolute LRC benefits for this two regimens are quite in reverse (16% vs. 19%). Considering relative LRC rates, CHART and DAHANCA-7 trials are almost equally beneficial (1.17 and 1.16) although the absolute LRC benefit for DAHANCA-7 is higher than for CHART. The PMH shows the LRC benefit similar to that for DAHANCA-7, but relatively to the control level it is more (1.30) effective than both DH-7 and CHART. These examples clearly show how important is the efficacy of standard regimen, to which altered regimen is compared.

If the control LRC is too low or too high, selection bias is likely possible or the results might also be influenced by the imbalance of known predictive and prognostic factors.

The next important point is which part of dose-response curve reflects the observed LRC benefit. If, for example, the control LRC of 30% is on lower and ascending part of the curve, 10-15% increase in the LRC for the tested arm needs probably higher increment in dose ($\Delta NTD_{2.0}$) than the same LRC benefit but reflecting steeper upper part of the curve. To illustrate this problem the LRC benefits representing only a part of the dose response curve are plotted against relative increase in the $NTD_{2.0}$ (Fig. 5). An average dose-response curve estimated for the segmental LRC curves is generally shallow (Fig. 5 – dotted line) and it suggests that in the majority of trials wide tumour and patient heterogeneity my bias the results.

Finally, the costs (CLE, LE) accounted for may decrease the LRC benefit, even below the standard LRC, although an overall therapeutic gain can still be observed as it is in the case of Cairo, Vancouver and EORTC 22851 trials. Therefore, therapeutic gain although noted might be misleading and in fact such trial should be considered as negative.

Is therapeutic benefit more expensive?

There is general belief that sophisticated altered regimens using more than one fraction per day or making „weekend busy" should automatically be more expensive, and they need higher total refund to cover an extra expenses of unconventional treatment. It is also argued that when shortening of overall treatment time by one or two weeks gives some savings, maintenance and staff costs to provide twice-a day treatment neutralize or even exceed such savings. Dische calculated that the CHART expenses are about 1000 pounds per patient higher than conventional irradiation [11]. The results of such calculation depend on whether they are considered as hospital budget, social or national costs or as a cost-effectiveness ratio. The last way seems the most realistic.

Considering various medicare systems, and exchange rates of currency in different countries, universal currency units (u) were used for the present analysis. They can easily be converted into dollars, pounds or zlotys (multiplying by the respective factor). Figure 6 illustrates the results of costs-effectiveness analysis and shows that if the costs of altered treatment are about 25% higher then standard total refund of hospital expences should also increase. However, when these costs are recalculated per one cured patient

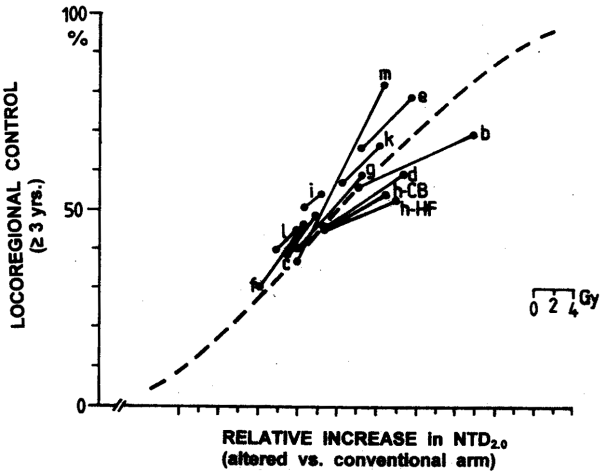

Fig. 6. LRC benefits plotted as a segment dose-response curves against relative increase in the $NTD_{2.0}$ ($\Delta NTD_{2.0}$) [dotted line is an average estimated dose-response curve]

the economic result of the expected therapeutic gain of 15% or 25% would decrease the expences at the national level by at about 10-25% (4545-3845/5000). The calculation is focused on radiotherapy only, and in the case of non-radical treatment extra costs of palliative radio-chemotherapy, surgery of failures, and terminal care are not accounted for the analysis.

At the level of hospital budget, if the total expenses are reasonably lower than total revenue to keep hospital on a good or at least safe economical condition, and the fixed costs (maintenance) and changeable costs (employment and wadges) are well balanced (i.e. 3:5) thus the hospital administration can easily calculate so called break-even point (Fig. 7), that means, the number of patients needed to balance annual costs. More patients admitted above this number will make profit to the hospital. If more expensive altered regimens are used (Fig. 7) then the more patients are needed to reach break-even, and overall financial profit will decrease. There is, of course, the risk that total expenses would not be balanced by the total refund leading to financial deficit. To keep hospital budget on acceptable and safe level it needs decreasing of fixed costs (about 5-8%), increasing the number of admitted patients, or reducing employment (the last alternative is sometimes impossible to realize if the number of employees is already restricted).

In summary, it seems important to know that the expenses of a new altered regimens in radiotherapy do not automatically lead to financial deficit of the hospital, and financial result strongly depends on the national health care economics and on the hospital financial policy. On the other hand, however, if altered (or any highly specialized) procedures are underpaid, there is a high risk that its effectiveness would decrease substantially (Fig. 9 – lower cube) or only a little but the risk of late effects (costs) will become unacceptably high due to treatment inaccuracy caused by less technicians employed or less money given to the procedure (Fig. 9 – upper – right cube). That means that the patient will be either uncured but without late complications or cured, however serious late effects may heavily threaten his quality of life. In both situations the result is not that which one would expect to achieve. This consequences have to be keep in mind by decision making administrators when they plan the costs of a single procedure and whole budget for the

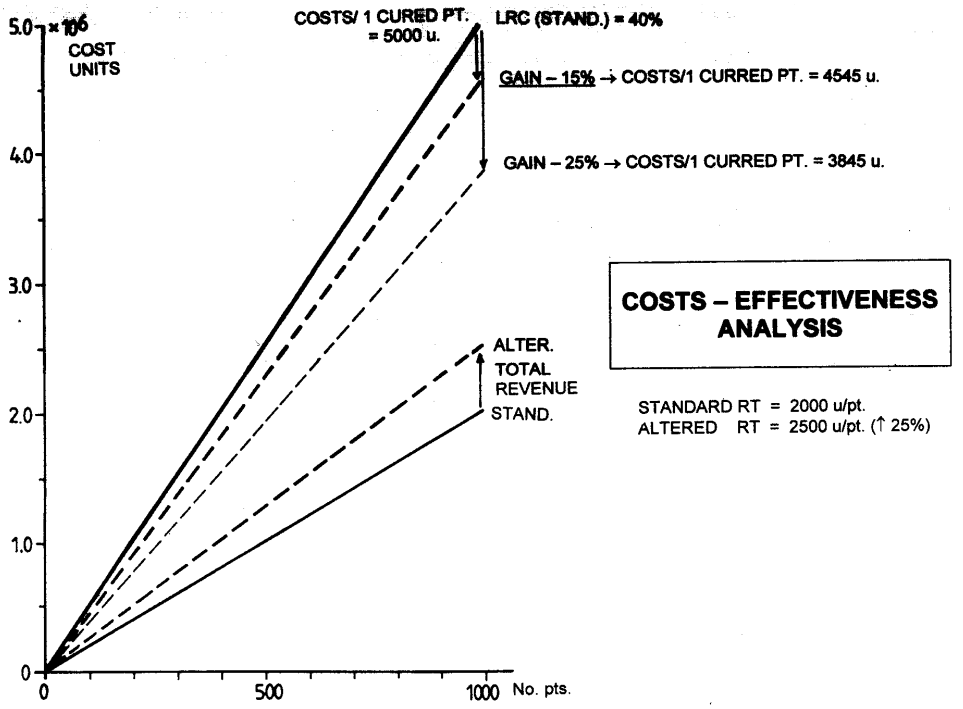

Fig. 7. Costs – effectiveness analysis of expenses of the standard and altered radiotherapy. Lower curves illustrate change in costs for altered vs. standard RT. Upper curves illustrate the costs calculated per one cured patients [u – represent universal currency unit which can easily be converted into individual national occurency]

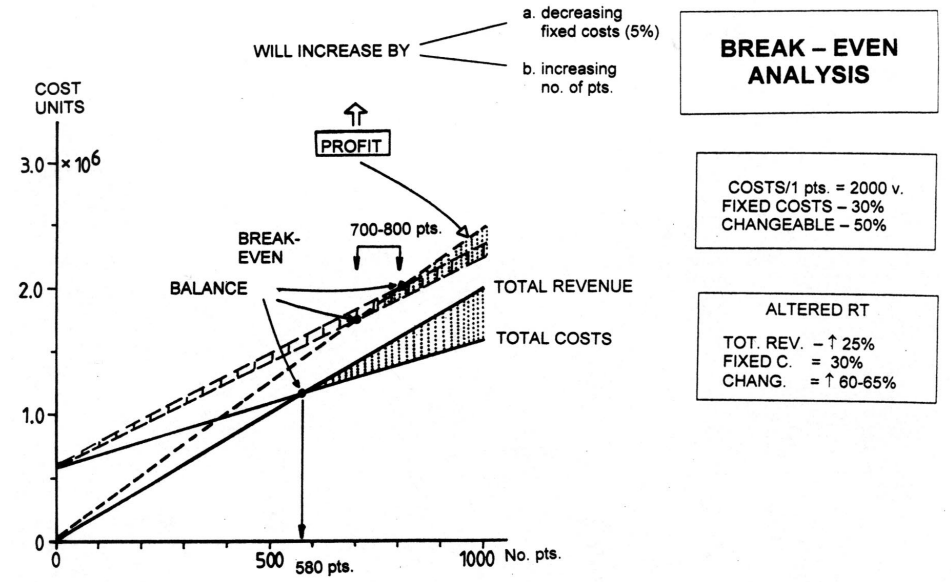

Fig. 8. Break – even analysis for overall hospital budget if altered fractionation regimens (dotted lines) is used instead of standard radiotherapy (solid lines). Break – even point represents the number of patients required to balance all expenses. The use of altered treatment with 25% higher costs needs extra 120-220 patients to balance the hospital expenses.

hospital. In the field of oncology, finances similarly to tumour biology and treatment strategies, follow the rules of „all or none" phenomenon.

Future perspectives and limitations

Present review of the 12 trials on altered radiotherapy for head and neck cancer leads to many uncertainties and doubts. Obviously the aim of all trials is to find an average „golden" key to treat various tumour stages and site, although in the majority of studies they have been groupped together. It appears there is not a single, answer, and perhaps different sites, stages and tumour differentiation needs different fractionation schedules.

Overall LRC benefit in favour of altered regimens is generally in the range of 5- 9 % with a wide variation in the increase in effective $NTD_{2.0}$, sometimes being not adequate to the LRC achieved. It is also possible the onset and quantity of accelerated tumour clonogen repopulation of 0.6 Gy/day is likely underestimated. The dose counterbalanced by repopulation could be at least 0.85 Gy, or even higher (1.1-1.2 Gy/day) during the weekends, and lag period might be shorter than 28 days, and 21 days

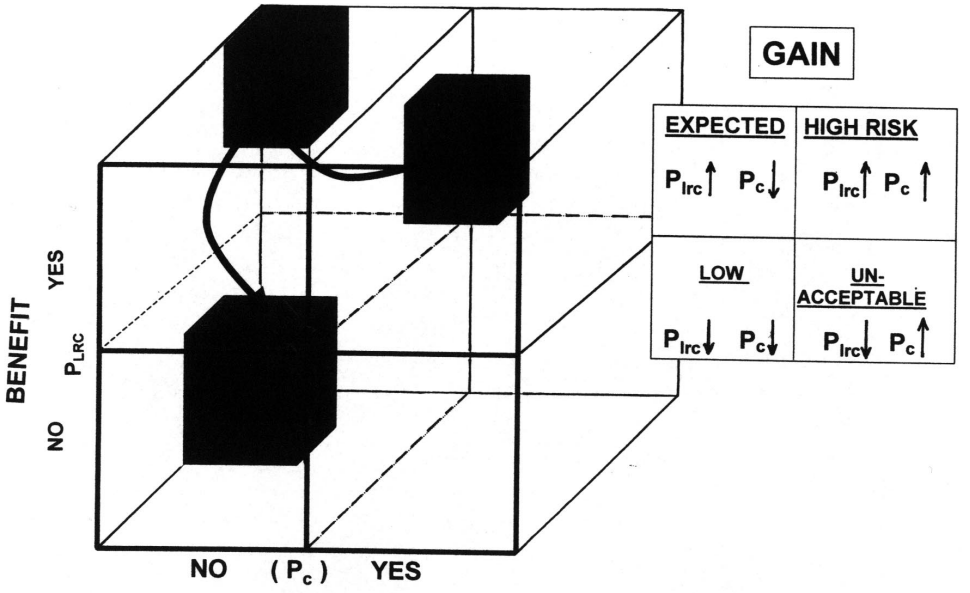

Fig. 9. „Two times two" decision – making square. Optimum benefit (the highest LRC with the lowest risk of late effects) can be expected for the most effective fractionation regimen and full refund of the hospital expences. The use of optimal treatment but with only partial refunding shifts the treatment to much less effective and/or higher risk of late complications.

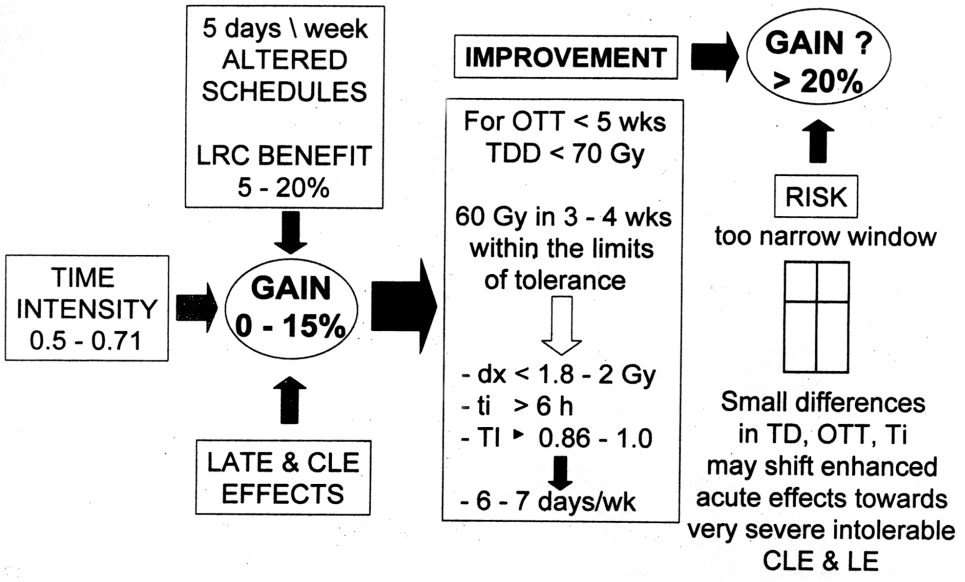

Fig. 10. Scheme of status of art of the benefit in favour of altered fractionation schedules and the proposed perspectives.

or even 14 days sound realistic. Consequently, the size of effective dose increment might be lower than reported.

Being back from the ranch of these 12-15 years of extensive studies to daily practice, only two or three altered regimens (DH-7, CAIR, concomitant boost) became a standard treatment. During these years we learned that time dilution is likely a significant enemy of dose intensity and the size of LRC benefit since only 0.71 of overall treatment time is effectively used in continuos irradiation during in 5 days a week, whereas it is clearly documented that any breaks during radiotherapy, therefore weekends also, are detrimental for treatment outcome. Furthermore, the LRC benefit can be lower than reported due to unprecise scoring and recording of late effects. But even if not, an overall therapeutic gain is moderate in the range of 0-15% (Fig. 8).

Despite many doubts and uncertainties, altered fractionation regimens still remain promising perspective. Because improvement in therapeutic gain may likely be seriously constrained by the intention to use total doses limited to the level of acute tolerance, there still should be a room for further dose escalation, with the reduction of treatment time. Kaanders et al. [3] suggest that doses around 60 Gy in 3-4 weeks are probably within the limits of tolerance (Fig. 8). The TROG 9101 trial with AHF schedule of 59.4 Gy given b.i.d. in 24 days producing the LRC rate of 54% for advanced head and neck cancers clearly supports this idea. It may be advantageous to escalate the dose towards the end of treatment when the mucosa is most actively repopulating [7, 8]. In order to spare late responding tissues the size of dose per fraction should be of less than 1.8 Gy, and then given b.i.d. with interfraction interval of at least of 6 hours (even about 12 hours for spinal cord). However, the use such schedule only 2- or 3 days-a-week generally produces negative therapeutic gain [23]. Even 5 days a week irradiation does not seen effective enough, and very intensive treatments can only be delivered escalating the dose beyond working days, that means, including weekends. In such case, time intensity would increase to 1.0 and may effectively enhance the effect of dose intensity to increase therapeutic gain. In this field, the DH-7 and CAIR results give intriguing perspective. Chemo- or brachytherapy acceleration at the end of treatment may also be considered.

It has to be remembered, however, that for such intensive treatments safe window is narrow, and small differences in time or dose of only few days or a few Gray can shift enhanced but still acceptable mucosal morbidity towards very severe and consequential intolerable late complications which may off-set sparing effect of altered fractionation [24]. When, the limit of acute tolerance is reached application of any potent agent which can prevent or diminish acute mucositis is of practical value. Unfortunately, drugs with sufficient potency have yet to be identified. Therefore, supportive care with corticosteroids, antibiotics, antiinflammatory drugs and parental nutrition, ordered early, may effectively diminish severity of acute effects.

There are about two decades of extensive randomized studies involving thousands of patients and producing interesting perspectives, but the question what should be the best modified fractionation regimen for specific tumour site and stage still remains widely open. Undoubtedly, individual patients and tumour characteristics need individual tailoring of the treatment regimen, and probably there are many keys, and therefore, there is a need of highly specific molecular and cellular predictors to find proper keys to proper doors.

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