Randomized clinical trial on 7-day-continuous accelerated irradiation (CAIR) of head and neck cancer – report on 3-year tumour control and normal tissue toxicity

Krzysztof Składowski\textsuperscript{a,*}, Bogusław Maciejewski\textsuperscript{b}, Maria Golen\textsuperscript{a}, Bolesław Pilecki\textsuperscript{a}, Wiesława Przeorek\textsuperscript{a}, Rafał Tarnawski\textsuperscript{b}

\textsuperscript{a}Clinic of Radiotherapy, Cancer Centre, Maria Skłodowska-Curie Memorial Institute, Ar.Krajowej 15, 44-101 Gliwice, Poland
\textsuperscript{b}Department of Radiotherapy, Cancer Centre, Maria Skłodowska-Curie Memorial Institute, Ar.Krajowej 15, 44-101 Gliwice, Poland

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Abstract

Purpose: To evaluate tumour and normal tissues 3-year response to 7-day-a-week continuous accelerated irradiation (CAIR) compared to a conventional treatment (5 days per week) in a randomized trial.

Materials and methods: One hundred patients with squamous cell carcinoma of the head and neck in stage T\textsubscript{2-4}N\textsubscript{0-1}M\textsubscript{0} were entered into the trial between December 1, 1993 and June 30, 1996. Dose per fraction of 2.0 Gy (to the end of 1994), and 1.8 Gy (since January 1, 1995) was the same in both arms and delivered once a day at regular 24-h intervals to total dose in the range of 66–72 Gy (depending on tumour stage). The only difference was overall treatment time being 5 weeks in the CAIR and 7 weeks in control arm.

Results: Actuarial 3-year local tumour control was 82% in the CAIR and 37% in the control group ($P < 0.0001$) with reduction in local recurrence rate of 83%. Actuarial 3-year overall survival was 78 and 32% ($P < 0.0001$), respectively. Confluent mucositis was significantly more severe and lasted longer in the CAIR than in control arm. After 2.0 Gy fractions five of 23 patients (22%) in the CAIR developed early necroses over a period of 2–4 months of follow-up which can be considered as a consequential to severe protracted acute mucosal reactions (CLE). For this reason dose per fraction was lowered to 1.8 Gy and the CLE was not observed again until now. Thus the overall rate of CLE decreased to 10%.

Conclusions: The gain in tumour control is likely the effect of shortening of overall treatment time by 14 days and regular continuous dose delivery during the whole course of radiation therapy including weekends. A 7-day schedule produces more severe acute mucosal reactions lasting longer than in conventional fractionation, however tolerable by patients. Relatively high rate (22%) of CLE in the 7-day arm observed during the first year of the study was eliminated by decreasing dose per fraction from 2.0 Gy to 1.8 Gy. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Acute and late radiation toxicity; Consequential late effects; 7-day fractionation; Head and neck cancer radiotherapy

1. Introduction

Over the last two decades the efficacy of many different accelerated, hyperfractionated, or combined fractionation schedules have been tested in a pilot and randomized clinical studies. Many of them, especially on head and neck cancer \cite{1,2,5,9,12-14,16,22,23,25,26,29,36}, document quite well the importance of time factor, postulated from many years as a major determinant of radiotherapy outcome \cite{4,11,19,20,24,27,37}, but only a few have shown convincingly that the use of altered fractionation could improved a therapeutic index \cite{13,25}. In general, the tumour cure as a result of accelerated fractionation has not been so high as we wished to expect, and an increased incidence and severity of acute mucosal reactions has often dominated. In the majority of these studies dose intensity was higher than in conventional fractionation and it may at least partly explain why acute normal tissue reactions occurred more frequently and were more severe. However, the wide spectrum of fractionation parameters used in accelerated and/or hyperfractionated regimes makes comparison of treatment results difficult in relation to changes in total doses, doses per fraction and interfraction intervals.

Therefore, in contrast to many other clinical studies, where fractionation parameters were modified with or with-
out reduction in treatment time, in the present clinical trial on head and neck cancer originally designed in Gliwice, overall treatment time (OTT) is the only variable. The idea was simple – to continue radiation during weekends. In this way, the OTT has shorted by 2 weeks, giving one fraction per day, 7 days a week (including Saturday and Sunday), without any change of the other dose-time parameters. This schedule defined as a continuous accelerated irradiation (CAIR) has compared to conventional 5-day treatment in randomized prospective study. The aim of the present report is to evaluate 3-year tumour response, survival and normal tissue toxicity.

2. Materials and methods

2.1. Patients characteristics

All 100 patients entered into two arms of a randomized clinical trial between December 1, 1993 and June 30, 1996 are included in the present analysis. Only patients with histologically proven squamous cell cancer of the oral cavity, oropharynx, supraglottic larynx and hypopharynx in stage T2–4N0–1M0, with age of ≤70 years, with good performance status (ZUBROD 0-1), haemoglobin level within the normal range and with no prior treatment were eligible for the trial. Patient and treatment characteristics (Table 1) show fairly uniform distribution of clinical, and physical parameters in both arms of the trial. Although CAIR group has more favourable oropharyngeal tumours (33 vs. 22%) and more N0 cases (64 vs. 53%), these differences are not significant. On the other hand, there was 7% more T4 patients in the CAIR group.

2.2. Radiation treatment

2.2.1. Fractionation schedule

In CAIR arm total dose of 66 ± 2 Gy for T2 and 70 ± 2 Gy for T3–4 tumours was given using one daily fraction of 2 Gy at 24-h intervals, 7 days per week including Saturday and Sunday, over 5 weeks. In control arm, conventional 5-day fractionation has differed by overall treatment time only, which was on average 7 weeks.

Unexpectedly high rate of mucosal necroses observed in the CAIR was considered as a consequential to severe acute mucosal effect [21]. It was the reason why the fraction size has been reduced from 2.0 to 1.8 Gy in both arms, since January 1995, with respective increase of total dose to on average 68 Gy for T2 and 72 Gy for T3–4 tumours (dose correction was calculated for α/β = 15 Gy). Thus, all fractionation parameters were kept the same in both arms, and 2-week difference in the OTT was maintained (Table 1).

2.2.2. Technique

All patients were treated with 60Co beams using two parallel-opposed fields. In the CAIR, ‘large’ fields covering PTV were used from Monday to Friday, and during Saturday and Sunday small fields (within the large one) limited to the primary tumour and involved node only (GTV) were irradiated. In control arm the small fields as a shrinking technique were used during the last week of the treatment. The spinal cord was excluded from the PTV after a total dose of 44–46 Gy. After off-cord reduction total dose to posterior neck nodes was supplemented up to 50 Gy using 9-MeV electrons. Elective lower-neck node irradiation was given to each patient except T2N0 patients with oral cavity cancer.

2.2.3. Dose specification and dosimetry

Dose distribution was optimized by computer treatment planning and the target absorbed dose (TAD) was specified at the reference point, according to the ICRU Report 50.
Dose distribution was routinely checked by in vivo dosimetry using the method proposed by Leunens [18]. The entrance (DEM) and exit dose (DXM) was measured for each patient at the first or second treatment session using p-diodes (Scanditronix) consisted of semiconductor detectors. TAD per fraction was calculated from the DEM and DXM values using the method proposed by Rizzotti et al. [28]. On average, the TAD per fraction was 1.4% larger than the prescribed dose, with a standard deviation of 3.2%.

2.3. Supportive treatment

In order to prevent breaks during the treatment patients with relatively early onset of the acute mucosal reaction rapidly progressing in severity (Dische system score ≥10) received anti-inflammatory drugs, local corticosteroids and antiseptic liquids. When severity of mucositis exceeded score 16, systemic corticosteroids and/or antibiotics were administered [32]. Systemic supportive treatment was given to 45 patients (90%) in the CAIR arm and to 24 patients (48%) in control arm, and it usually started on the end of second or third week of radiotherapy, and was discontinued when severe reactions began to heal and patient tolerance to treatment improved.

2.4. Endpoints and analysis

The aims and endpoints of the study were as follows:

- to compare acute and late radiation toxicity in both arms;
- to analyze local control and overall survival induced by the same total dose given in 5- or in 7-week treatment.

All endpoints were measured from the date of randomization. Follow-up is not longer than 52 months, with the median time of 37 months. Four patients out of 100 (4%) have follow-up shorter than 12 months.

To quantify tumour response and acute mucosal reactions all patients have been examined independently by the same four radiation-oncologists (two of them have been qualified specialists in both radiotherapy and otolaryngology) at least once a week during the treatment. Two of these examiners were not involved in the study. During the first 2 months of follow-up tumour and normal tissue response was evaluated every 2-weeks, and subsequently every month during the first year of follow-up. Further follow-up was every 2 months during second year and every 3–4 months thereafter.

2.4.1. Radiation toxicity

Acute mucosal reactions were scored using the modified Dische system, because it places emphasis on both morphological and functional effects, especially dysphagia and odynophagia and subjective reaction of individual patient to the given treatment [7,8]; scoring system was described in detail elsewhere [21]. Mean values of scores of all items made by four independent observers were added up and the mean value was taken as a measure of the both objective and subjective acute radiation effect.

According to Peters et al. consequential late effect (CLE) was defined as a type of radiation injury attributed to complete denudation of mucosal epithelium rather than for direct injury of the mesenchymal tissues associated with typical late effect [27].

Six months after completing the treatment was accepted as an earliest time of the occurrence of typical late effects which were recorded using the EORTC scoring system.

2.4.2. Local control

Patients with incomplete clearance of primary tumour or neck node were scored as relapsed at time zero and patients who died without evidence of local and nodal disease were censored at the time of death. Patients with incomplete follow-up were censored at the time of the last follow-up. Tumour or nodal recurrence was evaluated in the group of patients with complete T or N clearance.

2.4.3. Overall survival

This endpoint was defined as the time from randomization to the time of death from any cause. Other patients were censored at the date of last “alive” information.

2.5. Statistics

Statistical procedures of tumour control and survival were performed with the intention-to-treat principle. Actuarial local tumour control and overall survival curves were calculated by Kaplan–Meier method and the two-sided log-rank test is used to compare cure and survival rates between the CAIR and the control. Analysis of normal tissue toxicity was performed on the eligible patients, i.e. one patient terminated the treatment at the beginning of 3rd week of irradiation and had to be excluded from the analysis of acute toxicity.

2.5.1. Recruitment and randomization

Study protocol was officially accepted by Ethical Committee at the Institute of Oncology in Gliwice, according to national law regulation. At the end of diagnostic procedures, the only patients who signed written consent were qualified to the trial. Treating radiation oncologists did not know assigned treatment before putting the patient to the trial. Simple randomization stratified by tumour site and TN stage, with 1:1 allocation was made by phone by the officer of the Bureau of Trials at the Institute using random numbers. No patients dropped out after randomization.

2.5.2. Target sample size

The shortening of OTT by 14 days in the CAIR compare to control arm would increase tumour cure rate by restricting the time available for tumour cell proliferation. Assuming that an average dose balancing tumour clonogen repopulation during 1 day of treatment prolongation is estimated on 0.6 Gy [37], the dose in CAIR schedule would be effectively larger of 8.4 Gy than that in the control, what...
gives 12% of a 70-Gy treatment. Assuming an average value of $\gamma_{37} = 2$ for the steepness of dose-response curve of head and neck squamous cell carcinoma [3], it seems reasonable to expect from the CAIR about 24% improvement in local tumour control (LTC). Because the average values of 40% of LTC for head and neck cancer have been noted in Gliwice from many years [19,20,31], therefore, the expected rate of the LTC in favour of the CAIR calls accrual of about 100 patients in each arm of the trial (for significance level $\alpha = 0.05$ and power $1 - \beta = 0.90$, two-sided test) [30].

2.5.3. Trial monitoring
The Bureau of Trials at Centre of Oncology MSC Institute in Gliwice independently monitored the progress of the trial. The interim analyses were planned in two situations:
1. unexpectedly high treatment toxicity of the experimental arm (it was reported immediately after 1 year of the study [21]);
2. after completing 100 patients with median 3-year follow-up.

3. Results

3.1. Compliance with the treatment
Three patients (3%) have not completed the radiation treatment. One patient in the CAIR was excluded from the treatment after 14 days of irradiation because of intercurrent renal bleeding not related to the treatment; for this reason acute treatment toxicity is analyzed in the group of 99 patients. Another patient (CAIR) had an extremely severe acute reaction and treatment was stopped after week 4. The remaining one patient (control group) refused to continue the treatment because of acute toxicity after 6 weeks of irradiation.

In both arms 96% of patients received total dose in the range of $100 \pm 10\%$ of the prescribed dose. The OTT was prolonged by 1–2 day in four patients (8%) in the CAIR, and by 1–4 days for three patients (6%) in the control arm.

3.2. Tumour and nodal early response
Complete tumour regression at the end of treatment and during the first 3 months of follow-up was achieved in 88% (95% CI ± 9%) of patients in the CAIR and in 69% (95% CI ± 13%) in control arm ($P < 0.05$). Complete node clearance was 100% (95% CI ± 47%) and 78% (95% CI ± 17%), respectively, however this difference was not statistically significant (Table 2). After complete tumour regression local recurrence developed in 15 of 34 patients (44%, 95% CI ± 17%) in control group versus three of 45 patients (7%, 95% CI ± 7%) in the CAIR. Thus, the reduction of local recurrence rate (RLRR; reduction of local recurrence rate was calculated from the equation: RLRR = $1 - \frac{LRR_{CAIR}}{LRR_{control}}$) in the CAIR was 84% and this value is highly statistically significant ($P < 0.001$).

3.3. Local control and survival
Overall actuarial 3-year local tumour control (LTC) rate was 82% (95% CI ± 12%) in the CAIR versus 37% (95% CI ± 14%) in control arm (Fig. 1) Therapeutic benefit of CAIR over conventional treatment was highly significant ($P < 0.0001$, hazard ratio HR = 0.23, 95% CI 0.12–0.43). The benefit observed in favour of the CAIR is maintained independently on tumour stage and origin (Table 3). Although differences in the LTC rates between 2.0 Gy and 1.8 Gy regimes were not statistically different, the LTC benefit of the CAIR slightly decreased (from 50% to 39%) when the size of the dose per fraction was lowered. The

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Tumour clinical status at the completing the treatment and at the 3-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>CAIR (7fx/7 days)</td>
</tr>
<tr>
<td>Primary tumour</td>
<td>51 patients</td>
</tr>
<tr>
<td>Complete regression</td>
<td>45 (88%)</td>
</tr>
<tr>
<td>$P = 0.021$</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td></td>
</tr>
<tr>
<td>Persistent tumour</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Local recurrence$^a$</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>$P = 0.0001$</td>
<td></td>
</tr>
<tr>
<td>Neck nodes (N1)</td>
<td>18 patients</td>
</tr>
<tr>
<td>Complete regression</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Persistent node</td>
<td>0</td>
</tr>
<tr>
<td>Nodal recurrence$^a$</td>
<td>0</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

$^a$ Recurrence rate is calculated based on the number of cases with complete regression.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Three-year actuarial local tumour control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAIR (%)</td>
</tr>
<tr>
<td>All patients</td>
<td>82</td>
</tr>
<tr>
<td>$dx = 2.0,\text{Gy}^a$</td>
<td>85</td>
</tr>
<tr>
<td>$dx = 1.8,\text{Gy}^b$</td>
<td>79</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>72</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>86</td>
</tr>
<tr>
<td>Supraglottis and hypopharynx</td>
<td>82</td>
</tr>
<tr>
<td>T2</td>
<td>100</td>
</tr>
<tr>
<td>T3</td>
<td>90</td>
</tr>
<tr>
<td>T4</td>
<td>63</td>
</tr>
<tr>
<td>N0</td>
<td>88</td>
</tr>
<tr>
<td>N1</td>
<td>72</td>
</tr>
</tbody>
</table>

$^a$ Up to the end of 1994.  
$^b$ Since the beginning of 1995.
analysis of the LTC per T stage suggests the highest benefit of the CAIR for T3 (2.8-fold) and T4 tumours (2.5-fold difference). The LTC rates are closely related to overall 3-year survival which was 78% (95% CI ± 12%) in the CAIR and 32% (95% CI ± 14%) in control arm (Fig. 2). This difference was also highly significant ($P < 0.0001, \text{HR} = 0.35, 95\% \text{ CI 0.19–0.58}$).

### 3.4. Acute mucosal reactions

Based on the recorded scores of acute reactions the ‘severity-time’ curves were estimated for individual patients, and Fig. 3 shows an average pattern with 95% CI of mucosal reactions in CAIR and control group according to the Dische scale and time of observation during and after completing the treatment. The earliest mucosal reaction, mainly erythema, occurred at the beginning of second week of the treatment, rapidly progressing into spotted (mainly in control arm) or confluent (mainly in CAIR) mucositis between days 7 and 21. The level of confluent mucositis (CM) was reached 1.5 week earlier in the CAIR than in control group.

Table 4 presents incidence and severity (grade) of mucosal reactions. Incidence of severe CM (maximum Dische score > 15 or EORTC grade IV) was two times higher in the CAIR than in control group (62 vs. 26%). Although none of the patients in both groups needed tube feeding, CM in the CAIR patients were morphologically and functionally more pronounced than that in the control, and the CM level was maintained until the end of treatment (Fig. 3). This difference in severity called significantly more frequent supportive treatment in the CAIR (45 patients: 92%) than in control arm (24 patients: 48%).

### 3.5. Late normal tissue reactions

Slight and moderate late effects (grades I and II) such as mucosal dystrophy or mouth dryness did not considerably decrease the comfort of patient survival, and thus they have been grouped together with the cases without late effect (grade 0). During at least 3-year follow-up there were 86% of patients in the CAIR and 92% of patients in control arm without or with slight and moderate late reactions (Table 5). Late effects in grade III (oedema, fibrosis, and atrophy) occurred in acceptable rates in both arms (4 vs. 8%) and the difference was not significant. There was no

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**Table 4**

<table>
<thead>
<tr>
<th>Scores</th>
<th>CAIR arm (50 patients)</th>
<th>Control (49 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTCa</td>
<td>Dische</td>
<td></td>
</tr>
<tr>
<td>I° &amp; II°</td>
<td>≤10</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>III°</td>
<td>11–15</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>IV</td>
<td>16–20</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>3 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

* EORTC morphological scores approximately correspond with morphological component of the Dische scores.
severe late reaction (grade IV) in control compared to overall rate of 10% in the CAIR.

During the period when 2.0-Gy fractions were delivered in the group of 23 patients in the CAIR five patients (22%) with protracted healing of acute mucositis developed the early mucosal necrosis during the first 4 months of follow-up. In two patients it progressed into mandibular necrosis and in the remaining three patients into soft tissue necrosis of the mouth floor or retromolar trigone. All of them should be considered as a consequential (CLE) to the severe prolonged acute mucosal reactions. Necrosis always developed within small radiation field treated 7 days per week. Two patients were admitted to reconstructive surgery and they are doing well. Three other patients refused surgical intervention and they received anti-inflammatory drugs and antibiotics. Spontaneous complete healing was observed in two of them after 10 and 18 months of follow-up. The remaining one patient died because of haemorrhage from carotid artery. In our preliminary paper [21] seven patients with consequential soft tissue necrosis were reported, but at the time of that analysis two persistent tumours were misdiagnosed as a necrosis in spite of multiple biopsies during the first 6 months of follow-up. Since 1995, when the dose per fraction was reduced from 2.0 to 1.8 Gy no more CLE has occurred, and thus the overall rate of patients with the CLE decreased to 10% (Table 5).

4. Discussion

4.1. Therapeutic benefit

For the past 25 years many retrospective studies and clinical trials shown that an increase in tumour control can be achieved by shortening treatment time [1,2,5,14,22–26,29,36]. It indirectly suggests that tumour clonogen population might be one of the most important factors determining treatment outcome. The present results also support this suggestion. Overall 3-year LRC rate of 82%, survival rate of 78%, and 84% reduction in local recurrence rate strongly suggest that the 7-day-a-week schedule might be considered as a very effective accelerated treatment, particularly the majority of patients (81%) had advanced tumours (T3–4). An interesting is the fact that late (3-years) disease outcome strongly correlates with early tumour complete regression, and at the completing the treatment or during the first 3 months of follow-up a significant advantage of the CAIR over conventional 5-day treatment have already been noted.

Overall 45% therapeutic benefit of 7-day schedule is much higher than that noted in other trials [1,5,9,13,14,25,36]. The results of EORTC 22851 trial comparing 70 Gy in 35 fractions in 7 weeks (standard) to 72 Gy in 45 fractions in 5 weeks (AF/HF split-course) have showed that shortening of OTT by 2 weeks produced 13% gain in 5-year LRC and 24% reduction of local failure rate in favour of AF/HF [14]. However, there was no difference in overall survival between two arms and high rate of severe late complication makes this accelerated regimen unacceptable. In contrast to the CAIR trial, all head and neck sites, except hypopharynx, and all neck node stages were included into the AF/HF study from ten institutions. Although the AF/HF trial has completed, in fact, with the median 3-week treatment contraction, its therapeutic benefit was about three times lower than that observed in the CAIR. For the AF/HF, however, it is difficult to separate the effect of changes in the dose per fraction (2 Gy vs. three times 1.6 Gy daily) from that in interfraction intervals (24–72 vs. 4–12–72 h plus 2 week split). Furthermore, it should not be ignored that wide variation in tumour sites, T and N stages, and some differences between centres in technical and dosimetry parameters may dominate over the effect of treatment schedule. Thus, it may flatten the dose-response relationship and dilute the gain from AF/HF treatment [3].

In contrast, the CAIR trial included fairly homogenous clinical characteristics of the patient population and fractionation parameters, among which OTT was the only variable. The tumour stage and site distribution was almost well balanced between CAIR and control arm. We believe that even more favourable oropharyngeal tumours and N0 cases noted in the CAIR group could not have any impact on the CAIR advantage over the standard treatment because this difference has been not significant, and, on the other hand, more unfavourable T4 tumours were in CAIR group. The reason why N0 and single node cases (N1) were only selected to the trial is that we wanted to have a clinical model clearly uniformly designed to study the efficacy of 7-day fractionation. Furthermore, multiple or large neck nodes may not only influence geographical misses and uncertainties in dose delivery but may also modify the response of primary tumour [35]. Thus, therapeutic benefit of the CAIR is addressed to T3–4N0–1 cases only, whereas AF/HF advantage

### Table 5

Late normal tissue reactions (LNTR)

<table>
<thead>
<tr>
<th>Severity score (EORTC)</th>
<th>CAIR arm</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dx = 2.0 Gy</td>
<td>dx = 1.8 Gy</td>
</tr>
<tr>
<td>Grade 0–II</td>
<td>17 (74%)</td>
<td>27 (96%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>5 (22%)</td>
<td>0</td>
</tr>
</tbody>
</table>
was mainly addressed to the most unfavourable T and N combinations [14].

Two of the most often cited trials in radiotherapy in recent years are the EORTC 22791 and the CHART [9,13]. The first one compared 80.5 Gy in 7 weeks (HF) against standard 70 Gy in 35 fractions also over 7 weeks [13]. Assuming $\alpha/\beta$ ratio in the range 10–25 Gy, the HF arm represents 7–11% escalation of the biologically equivalent dose in 2-Gy fractions, and it gave significant increase in 5-year loco-regional control of 18% (56 vs. 38%), with a significant improvement of the overall survival. The observed benefit of the HF over standard schedule is mainly the result of dose escalation without change in the OTT.

An intensive short course of CHART was designed by reducing the OTT to 12 consecutive days, and giving 1.5 Gy fraction t.i.d. to the total dose of 54 Gy [9,29]. No increase in late morbidity was noted, but negative effect of lower total dose has balanced the positive effect of OTT contraction resulting in no changes in LTC and survival. However, some therapeutic gain in favour of T$_{1-3}$, well-differentiated cancers of the larynx has been reported.

Princess Margaret Hospital (PMH) trial tested AF schedule of 51 Gy in 20 fractions versus HF regimen of 58 Gy in 40 fractions with the same OTT of 26 days in both arms [5]. The interim results reveal no significant improvement of 3-year LTC of 5% in favour of the HF arm; the significant benefit has been dedicated only for tumours of less than 4 cm. An interesting point is that, in fact, these two fractionation schedules differ by only 2–3.5 Gy of the BED normalized to 2-Gy fraction (for $\alpha/\beta$ ratio in the range 10–15 Gy).

From all of the above trials one obvious conclusion should be again underlined – the therapeutic benefit associated with OTT contraction can only be guessed indirectly because of variation in fractionation parameters. The radiobiological design of several AF schedules has been generally based on more or less theoretical assumptions for changes in total dose, dose per fraction, number of daily fractions, and even small changes in $\alpha/\beta$ ratio and $\gamma_{50}$ values might be a potential sources of bias [3]. Furthermore, almost all trials, except CHART, used traditional 5 days a week to treat the patients with different number of daily fractions, whereas in the CAIR, patients were irradiated regularly, every 24 h, including weekends, and the OTT shortened by 2 weeks was the only variable. Therapeutic gain of 45% in 3-year LTC in favour of CAIR may suggest that continuous irradiation during 72-h weekend might have an important impact on the treatment outcome.

The only trials to which the CAIR can simply be compared are the DAHANCA-2, 5 and 7, where the OTT was also the only fractionation variable [25]. These series of consequent and elegant studies performed in one country demonstrate how the reduction in the OTT improves LTC of head and neck cancer. Total dose of 66 Gy in 33 fractions was given either as a split-course in 9.5 weeks (DAHANCA-2), conventional fractionation in 6.5 weeks (DAHANCA-5) or accelerated fractionation in 5.5 weeks (DAHANCA-7). In the 5.5-week treatment the sixth fraction was given on Saturday or as a second daily fraction on Friday evening. Avoiding uncompensated 3 weeks split 3-year LTC increased 20% (from 32 to 52% – DAHANCA 2 vs. 5). Further a 1 week reduction of the OTT, to 5.5 weeks, resulted in a significant increase in the LTC of the next 10% (from 52 to 62% – DAHANCA 5 vs. 7), what gives on average 1.5% improvement in the LTC per each daily reduction of the OTT below 6.5–7 weeks. CAIR schedule by giving seven fractions in 7 days goes almost two steps further - reduces the OTT from 7–8 weeks to 5–6 weeks and completely eliminates the weekend breaks. Thus, the shortening of OTT by 2 weeks and regular irradiation every 24 h in the CAIR produces, on average, 3.2% improvement of 3-year LTC per 1 day contraction. This is a little bit higher than the median value calculated by Fowler et al. from retrospective data of 5-day treatment [11].

The DAHANCA trials [25] showed alike a benefit of accelerated regimen is mainly related to well differentiated tumours, and seems to be lost with progressing of dedifferentiation of the tumour. This impact of tumour grade on outcome was also observed in the CHART [9]. In the CAIR tumour grading was not established in all cases and it does not allow quantify grade-fractionation relationship.

One may argue that results of control group (37% of overall LTC rate) are below average expectation. Perhaps it could look such from the Western point of view where the patient selection criteria to radiotherapy alone are a few different than in Middle–East Europe. It is clear for us that the relative number of under-fed, heavy smoker patients with advanced, deeply ulcerated T$_{3-4}$, head and neck cancers treated by radiation in Gliwice is higher than that observed in EC countries or in US and Canada. Furthermore, our previous papers have indirectly mentioned this unfavourable tumour distribution and showed very clearly that the 40% rate of LTC for head and neck cancer is a stable overall limit of conventional irradiation in Gliwice from many years [19,20,31].

Another intriguing question is whether 10% reduction in fraction size might also reduce therapeutic benefit already noted? When we look at the LTC rates noted for the 2.0 and 1.8 Gy (Table 3) and related median increments of OTT (Table 1) we can find that 4-day prolongation led to a 6% decrease of LTC in CAIR arm whereas 3-day longer conventional treatment led to a 5% increase in LTC. It has produced that LTC benefit of the CAIR decreased by 11%, from 50% to 39%. To explain this issue other than by hazard is not possible, however, there is no doubt that 3-year follow-up could be considered as too short. Assuming that about 90% of local recurrences generally occur during this period, and even if the LTC rate would decrease by about 5–10% during the next 2 years the therapeutic benefit of 35–40% will still be high.

4.2. Acute toxicity – how the game is played?

In many trials the rate of CM is similar, although they represent wide variation in fractionation parameters. In the
EORTC 22791 67% of CM was documented [13]. The same rate but with delayed healing was found in the EORTC 22851 [14], similar 62% rate in the CAIR, and 73% in CHART with 30% persistent CM lasting longer than 6 weeks [9]. At first glance, it looks that although OTT being in a wide range, from 12 days to 7 weeks, does not produce sparing effect on the incidence of CM with treatment protraction. However, regular weekend breaks and any planned or unplanned gaps during the treatment significantly improve regenerative response and healing of acute reaction as the mucosa is a fast regenerating tissue and repopulation can balance daily doses of about 1.8–2.0 Gy [6,10,17,33,34].

There was an interest on accumulated dose per week (AD) as a parameter, which may characterize the incidence and severity of acute effects. Based on the conclusions from Fletcher et al. [10] and Denham et al. [6], Kaanders et al. point out that in most patients the mucosa can not compensate dose greater than 10 Gy per week [17]. It does not seem true. In the study of Van der Schueren et al. the AD of 22.4 Gy or 30 Gy produced fairly severe CM [34]. However, these various split-course schedules had treatment rest periods long enough to allow complete healing of the CM. After 16 Gy accumulated in 2 days with a 12-day break thereafter, acute effect did not transgress the level of spotted mucositis. Even the AD of 24 Gy in the EORTC 22851 [14] or 31.5 Gy in the CHART [9] did not result in extremely high incidence of CM, whereas 14 Gy in CAIR was too much [21]. It may suggest that the AD is, by itself, not a good characteristic for the incidence and severity of the CM. It seems likely 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? Analysing advantages and disadvantages of the EORTC 22851 trial [14] and the CAIR [21] Kaanders et al. suggested that none of many clinical and physical parameters could satisfactorily explain the greater toxicity of CAIR [17]. However, despite the fact that the AF/HF was split-course schedule, the most important difference is that it was ‘weekend-free’ treatment, whereas the CAIR was ‘weekend-continued’. It seems that regular 24-h intervals between 2-Gy fractions given continuously over 5 weeks were not long enough for mucosal cell repopulation to compensate progressive denudation of epithelium, which has led to persisted severe mucosal reaction finally progressed into consequential necrosis in 22% of patients. In the AF/HF study 12–14 days of rest period after 28.8 Gy in 8 days and regular weekend breaks during the dose delivery likely allowed the mucosa to compensate radiation injury. On the other hand, 4-h intervals between three daily fractions might be insufficient for complete repair of sublethal damage and it resulted in an unacceptable rate of late effects [33]. Nguyen et al. used 2-h intervals between eight daily fractions delivered over 5 days and repeated after 2-week rest period, and it produced 26% rate of CM with ulceration, that in 23% of patients progressed into severe necrosis [22]. Perachia et al. observed even worse consequences after 48–56 Gy given in 2-Gy fractions over 8–12 days with 4-h intervals [26]. The severe CM developed after 2–3 weeks from the beginning of treatment and within 4–5 weeks led to deep necrosis in 68% of patients, being the cause of death in nine patients (41%) with complete tumour clearance. A slightly lower dose per fraction of 1.8 Gy was reported to produce acceptable mucosal reactions, however in a small study-group of nine patients [12]. The same effect was noted in CAIR (but in a larger group of patients), and when the fraction size was reduced by 10% (from 2.0 to 1.8 Gy) no more consequential ‘late’ effects occurred until now. Analysis presented in our previous paper specifically concentrated on consequential effects in the CAIR showed that they tended to occur in younger patients, with a greater weight and haemoglobin loss during the treatment, more likely treated with larger fields [21].

Overgaard et al. also observed that tumour volume and field size has a significant influence of radiation morbidity [25].

All these results show that neither total dose, OTT nor AD by itself could simply correlate with the risk and severity of acute mucosal reactions. During the radiation treatment several factors influence the ‘meaning’ of the AD value, i.e. presence or lack rest periods, size and number of daily fractions or length of interfraction intervals. Thus the AD of 20 Gy for ‘weekend-free’ schedules, or even larger values (22–30 Gy) for split-course treatment produces tolerable level of severity and acceptable incidence of acute mucosal reactions, whereas AD of 14 Gy for ‘weekend-continued’ regular treatment is too much and too risky.

The results of the 7-day irradiation show very high therapeutic gain within a relatively small group of 100 patients, which could not be then considerably enlarged. The reason is following: when the interim analysis was prepared unexpected therapeutic gain in the CAIR had warranted the decision to close conventional-control arm due to ethical principles. Thus, it is obvious that sample size of CAIR trial has increased the likelihood to get by chance such a high gain, and tends to interpret and display the conclusions with caution.

From January 1, 1998, 7-day schedule has been the standard in-patient treatment in Gliwice for majority of head and neck squamous cell cancers. But the fractionation study is still ongoing. Since July 1, 1995 an extra arm has been introduced into the CAIR trial. Seven fractions of 1.8 Gy are given 5 days per week by concomitant boost schedule (twice-a-day treatment with 6–8 h intervals on Tuesdays and Fridays) with the same total doses and OTT as in the CAIR. The purpose is to evaluate an impact of weekend gap on tumour control and kinetics of acute mucosal reaction comparing with CAIR arm.

5. Conclusions

The present trial has showed that continuous accelerated
7-day treatment provides significant therapeutic benefit for T2,N1a head and neck cancer in regarding of both local control and overall survival. Fractions of 1.8 Gy keep acute mucosal reaction on tolerable level. Results of CAIR and recent trials suggest that one may expect improvement in loco-regional control using dose escalation with sufficiently long interfraction intervals, with dose per fraction of less than 2 Gy and overall treatment time of 5–6 weeks. However, such accelerated and/or hyperfractionated schedules can only be realized if the treatment facility will operate beyond normal working hours or even weekdays. Nevertheless, the question what could be the most effective altered fractionation schedule for specific tumour site, stage and grade remains still open.

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