Split-course accelerated hyperfractionation (CHA-CHA) for advanced head and neck cancers – preliminary results

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The purpose of the study was to evaluate toxicity and effectiveness of the split course, accelerated hyperfractionation with a planned gap (CHA-CHA) on a base of the pilot group treatment results.

The material consisted of 27 patients with advanced (T_2 N_{2c-3}, T_{3-4} N_2), oral cavity, oro- hypopharynx and larynx cancers, irradiated with a df 1.6 Gy twice a day, with 6-hour gap, up to TD 64 Gy in 28 days, with 8-day gap in a middle. Mean tumor dimensions were 4.2 and 3.9 cm in X and Y axes, respectively and mean nodes dimensions 3.9 cm in both axes. The course and intensity of the mucositis were evaluated in the Dische scale together with the degree of a tumor and nodes regression. Survival analysis and dependencies evaluation between physical/biological factors and treatment results were performed.

The mucositis intensity was high from 2nd to 5th week (the highest mean – 15 Dische points in 4th week), but on acceptable level. 54.5 % of CR of the tumor and 57.1 % of nodes were noted. Survival analysis showed 44 % of a 2-year and 35 % of a 4-year OS and 44 % of a 2-year and 38 % of a 4-year survival excluding deaths from distant metastases. Correlation between the hemoglobin level and the nodal regression two months after the radiotherapy (p=0.01), the tumor diameter and TCP (p=0.047), and OS and the nodes diameter (p=0.004), the PS (p=0.02) and the hemoglobin level (p=0.04) were found.

CHA-CHA could be a valid method in advanced head and neck cancer treatment but its efficacy should be confirmed in randomized phase of trial.

Key words: altered fractionation, accelerated hyperfractionation, split course, head and neck cancers, radiotherapy

The altered fractionation trials were designed in response to unsatisfactory results and overall lack of progress obtaining after conventional radiotherapy of head and neck cancer patients. By virtue of our design we sought an increase in therapeutic gain understood as a cure rate improvement and a complications percentage decrease. Insofar as concerns radiobiological research, the aforementioned trials' main impact resides in our having ascertained the value of fraction dosages and the time factor involved in a course of radiotherapy [20]. It was found that a decrease in fraction dose (fd) reduced the possibility of adverse effects, and that a decrease in the overall treatment time (OTT) improves the cure rate. Of substantial influence was a second phenomenon, rapid tumor clonogen repopulation starting from day 28 of the treatment, decreasing lethal radiotherapy effect about 0.6 Gy per day [11, 20].

The main and at present routinely employed altered schemes of dose fractionation such as hyperfractionation [5], accelerated fractionation [5, 8] and combinations of both, had been established in the nineteen-eighties and nineteen-nineties. Some of most popular combinations are: CHART (Continuous Hyperfractionated Accelerated Radiation Therapy) – three daily fractions of 1.5 Gy, up to a total dose (TD) of 54 Gy delivered over 12 days (3); CB (Concomitant Boost) – a boost delivered as a second daily fraction through part of the treatment [1, 6], CAIR (Continuous Accelerated Irradiation) – 1.8 Gy of fd delivered once a day, seven days a week, up to TD of 72 Gy [10, 18]; and irradiation using fd of 2 Gy, once a day, six times a week, up to 66 Gy [15].

The radiotherapy modalities described above give improved treatment results in some groups of patients, but loco-regional advanced head and neck cancers (T_2 N_{2c-3}, T_{3-4}

N_2) remain a huge therapeutic problem. The cure rate in this group is low and often near to zero. The application attempts of presented schemes and the combination of radio and chemotherapy did not give satisfactory results [17]. The unexpected three-years survival of 80 % of the patients in the group $T_{2-4}N_{0-1}$ treated with CAIR warranted the design of the new fractionation scheme, which is based on a combination of hyper- and accelerated fractionation with planned gaps. The rationale for it was the delivery of possible high TD with a high dose intensity in an OTT of less than 28 days in order to avoid an accelerated clonogen repopulation, and with a planned gap in the middle of the treatment to allow for mucosal cell damage repair and repopulation, and for the improvement of treatment tolerance. On this basis we have created the new fractionation modality called CHA-CHA (doubled CHART).

The aim of this study is a toxicity and effectiveness evaluation of the continuous accelerated irradiation with a planned gap (CHA-CHA) of advanced head and neck cancer patients, based on pilot group treatment results.

Material and methods

Patients. The analyzed material consisted of patients formed into a pilot group for the second phase of clinical trial evaluating the treatment toxicity. The inclusion criteria were: a microscopically confirmed squamous cell cancer (SCC) in stage T_2N_{2c-3}, $T_{3-4}N_2$ in one or more of the following: the oral cavity, the oro-hypopharynx, and the larynx; age between 20 and 70 years; performance status Zubrod 2, and no previous treatment for neoplastic disease.

The material consisted of 27 consecutive patients (22 men, 5 women) suffering from advanced inoperable head and neck cancers, referred to our department and irradiated with a curative intention using the CHA-CHA scheme. Patients were treated in the radiotherapy department of M. Sklodowska-Curie Cancer Center in Gliwice for a period of 3.5 years (from 1998 to 2002). Patients were aged from 44 to 70 (mean 56). All of them were hospitalized during the radiotherapy. The most common diagnosis was oropharynx cancer (11 cases); 9 patients suffered from larynx, 6 from tongue and 1 from hypopharynx cancer. For precise stages of disease, see Table 1.

Table 1. The number of patients in particular disease stage

TNM stage	Number of patients
T_2N_{2c}	2
T_2N_3	1
T_3N_{2b}	1
T_3N_{2c}	2
T_3N_3	1
T_4N_{2a}	1
T_4N_{2b}	8
T_4N_{2c}	6
T_4N_3	5

The stage of the disease was assessed on the bases of a physical and laryngological examination, a directoscopy, a head and neck CT, and a cervical lymph nodes ultrasonography (USG). In all cases a chest X ray and USG of the abdomen were performed. Dimensions of primary tumors and enlarged lymph nodes were measured using the aforementioned examinations. Dimensions of tumors ranged in X and Y axes between 2 and 6 cm (means respectively 4.2 and 3.9). Dimensions of the biggest node ranged between 1 and 10 cm in X-axis and between 1 and 9 cm in Y-axis (means in both cases were 3.9).

In 18 cases only was the cancer differentiation degree evaluated. In 2 cases it was G I, in 11 cases G II, and G III in 5 cases.

The majority of patients when beginning treatment were in a good performance status. In 9 cases it was assessed as Zubrod 0, in 17 as Zubrod 1 and only in one case as Zubrod 2.

The average body weight at a beginning of the radiotherapy was 66.2 kg; the average hemoglobin level 14.2 g % and ranged between 10.8 g % and 15.4 g %.

Treatment. The protocol of this phase CHA-CHA clinical trial was approved by the Ethics Committee of Oncology Institute in Gliwice 4. XII. 1998.

Rationale for such radiotherapy modality was described in the last part of introduction. The CHA-CHA schedule is based on delivering 1.6 Gy twice a day with a 6-hour gap enabling sublethal damages repair, up to TD of 64 Gy in 28 days with an 8-day gap in the middle of treatment (from 11th to 18th day). The rationale for the planned gap was an attempt to use the difference between the repopulation kinetics of the tumor and normal tissues cells, which could improve healing of acute mucositis without a decrease of cure rate.

Precise comparison of the CHA-CHA schedule to the conventional fractionation considering tumor cells radiobiology is very difficult. Taking into account very high α/β value, ranging up to 25–50 Gy [11], the impact of fraction dose change is rather negligible. Probably, the most important factors are the OTT and its derivative – dose intensity (DI) defined as TD and OTT ratio. DI for CHA-CHA – 2.29 Gy/day, is 1.6 times bigger than for the conventional fractionation (1.44 Gy/day – 72 Gy in 50 days). If we consider the conventional treatment as 72 Gy delivered in 2 Gy fractions in 50 days, we find 22 days of OTT difference between it and CHA-CHA. For the conventional fractionation, the dose equivalent to each 1 day of OTT extension over 28 days, for different head and neck cancers varies from 0.50 Gy to 0.78 Gy [11]. When multiplying these values by OTT difference, we can calculate theoretical gain in TD, which ranges from 11 Gy to 17.2 Gy. This comparison shows that dependently on tumor kind, biological equivalent of CHA-CHA TD varies from 75 Gy to 81.2 Gy. Used above values of dose increment required for 1 day treatment prolongation were calculated mainly on the base of patients irradiated using fd of 2.3 Gy to 2.7 Gy up to TD from 57.5 Gy to 67.5 Gy [11]. There are some hypotheses that during longer treatment, as for example

72 Gy in 50 days, the repopulation of tumor clonogen cells could increase, and necessary TD increment for each 1 day of OTT prolongation could be higher than aforementioned values. In such case the biological equivalent of CHA-CHA TD can be even higher than above calculated.

All patients were irradiated using high-energy photons X generated in a linear accelerator (Clinac 600), from two opposite coaxial fields on the base of 3D conformal plans.

The size of irradiated fields ranged between 119 and 270 cm^2 (mean 184). Fields were reduced according to the treatment plan (sparing the spinal cord) after a dose of 35.2 Gy. After the field shrinkage, the posterior lymph nodes chain was irradiated up to TD of 50 Gy using 9 MeV electrons. Upper and medial, anterior cervical lymph nodes were irradiated up to 60.8 Gy. The last 3.2 Gy were delivered for the boost field. The lower neck and supraclavicular region were irradiated conventionally, 2 Gy per fraction up to 50 Gy. In 9 cases, in which an incomplete regression of the involved lymph nodes was found, the additional boost for this region was delivered using fd of 2 Gy or 3 Gy up to TD of boost ranged from 9 Gy to 27 Gy.

In all cases *in vivo* measurements of entrance doses using semiconductor dosimeters and on line field geometry checks using the Portal Imaging System were performed. Differences between planned and measured entrance doses varied from –5 % to 3.5 % (mean 0.2 %, SD±1.7). The acceptable value of an entrance dose error was ±3 %. Bigger discrepancies were immediately corrected. In all cases, the geometry of an irradiated field was in accordance with the simulated one. The shift between them ranged from 0 to 4 mm (mean 1.1 mm, SD±1.7). The maximal acceptable shift was 5 mm.

One patient finished the treatment on the dose of 32 Gy because of pneumonia. This patient was excluded from the further analysis. Remaining patients were treated systematically according to protocol of the trial.

To prevent a pronounced mucositis, vitamin C was ordered from the start of radiotherapy; from the 5th treatment day non-steroid anti-inflammatory drugs; antibiotics from the 10th, from the 18th anti-mycotics and steroids; and from 23th intravenous fluids were delivered. In no one case was an alimentary tube used and in no one case was the treatment interrupted due to radiation mucositis.

Follow up evaluation. All patients were examined at least once a week up to the twentieth week from the radiotherapy start. During an examination, patient's weight was measured and the intensity of the mucosal acute radiation injury was evaluated in Dische scale [3].

Curves were plotted according to the acute effect intensity for particular patients. An average was calculated of the intensity of mucosal reaction in weeks following up to the tenth week, and an appropriate plot was constructed.

At the end of the treatment the hemoglobin level and the body weight were measured.

The degree of tumor and lymph node regression was evaluated at the treatment completion, one and two months after the radiotherapy, and at the time of last control. The degree of the regression was assessed according to the following scale: 1 – complete regression, 2 – 90 %–99 %, 3 – 50 %–89 % regression, 4 – regression less than 50 %, and 5 – no response or progression. Patients were qualified to particular degrees on the bases of a physical examination, USG and CT.

Statistical methods. Mean and median of follow up were calculated. Overall survival (OS) and survival considering only deaths caused by locoregional progression were evaluated using the Kaplan-Maier method.

The character of particular changes distributions was checked using the Shapiro-Wilk test. Correlations between regression degrees during following controls and biological factors such as age, grading, performance status, tumor and node diameters and hemoglobin level were checked using the Spearman test. Using an analysis of the logit regression, dependencies between tumor and node sizes and the locoregional control were evaluated.

The proportional hazard Cox model was used to assess dependencies between survival and tumor and node diameter, performance status, hemoglobin level at the beginning of radiotherapy, and tumor and node regression directly after the treatment completion one and two months after the treatment.

Results

Means of acute reaction intensity in following weeks and their changes are presented in Figure 1.

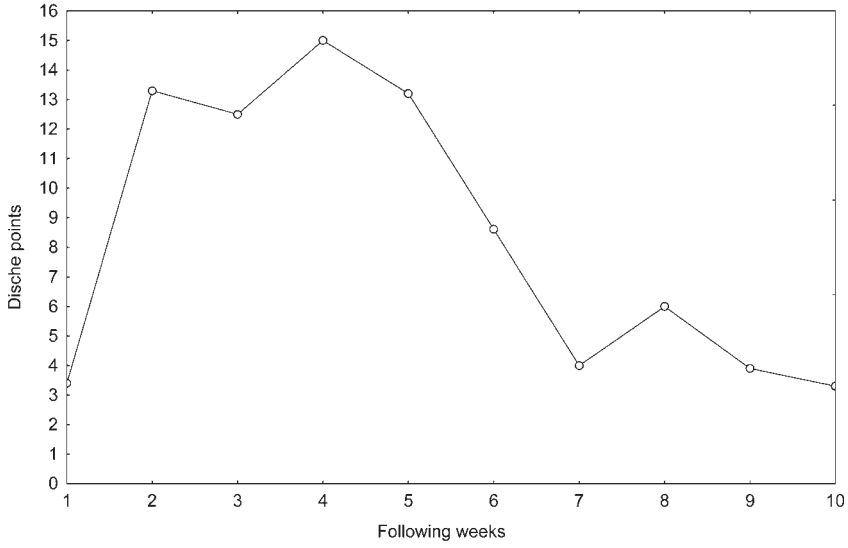

Figure 1. The course of a mean acute reaction intensity in following weeks.

Consequential late effects have appeared in no one case.

The level of hemoglobin measured at the end of the treatment ranged from 10.7 g % to 15.2 g %. The mean hemoglobin level (13.1 g %) was 1.1 g % lower than at the beginning of the treatment.

Body weight during the last week of radiotherapy ranged from 48 kg to 89.1 kg (mean 63.8 kg). Such results show that the average patient's weight decreased 2.4 kg during treatment, the reason being the intensity of the mucositis and related trouble with swallowing, resulting in patient malnutrition.

The tumor and enlarged lymph nodes regression assessed during following controls is shown in Table 2.

A period from the radiotherapy completion to the last control ranged from 0 (one case) to 53 months (mean 17.6).

Table 2. The percentage of tumors and metastatic lymph nodes in particular regression degrees during following controls

Degree of regression	1	2	3	4	5
			The last day of treatment		
Percentage (tumor)	26 %	15 %	33 %	26 %	0 %
Percentage (lymph nodes)	15 %	8 %	38 %	35 %	4 %
			1 month after radiotherapy		
Percentage (tumor)	23 %	27 %	35 %	15 %	0 %
Percentage (lymph nodes	24 %	0 %	40 %	32 %	4 %
			2 months after radiotherapy		
Percentage (tumor)	41 %	18 %	32 %	9 %	0 %
Percentage (lymph nodes	28,5 %	5 %	33 %	28,5 %	5 %
			The last control		
Percentage (tumor)	54,5 %	4,5 %	14 %	9 %	18 %
Percentage (lymph nodes	57,1 %	0 %	14,3 %	14,3 %	14,3 %

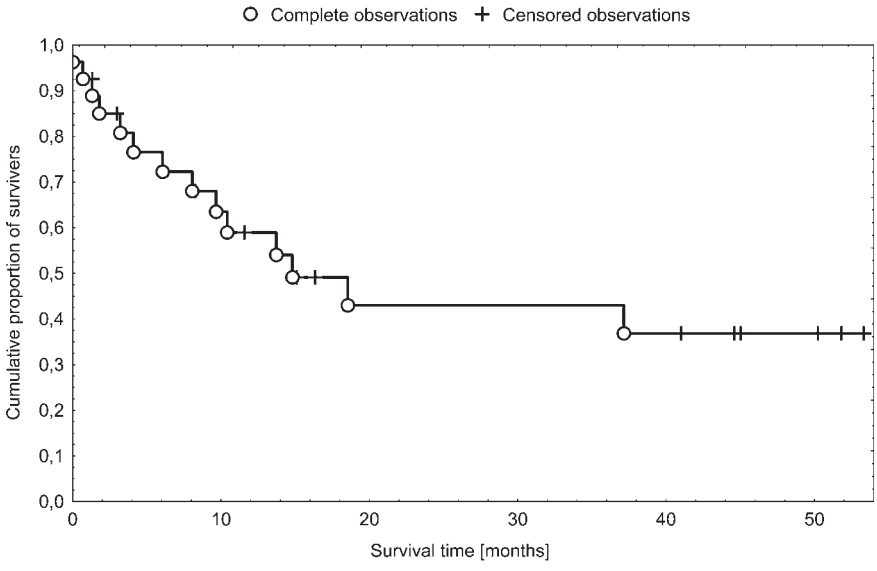

Figure 2. The overall survival analysis.

Some patients were lost from observation, so follow up calculated to the time of death is longer and ranges up to 53.3 months (mean 20.2, median 15.1).

Fourteen patients died, 12 due to locoregional progression and 2 due to distant metastases. Nine patients are still alive, of which 8 show no sign of neoplastic disease and 1 with distant dissemination. Four patients were lost from observation, but as regards the cause of their death, there were no exact informations available.

A survival analysis using the Kaplan-Meyer method showed 44 % of the 2-years and 35 % of 4-years overall survival (Fig. 2). The same analysis used for an assessment of a survival excluding deaths from distant metastases gave 44 % of the 2-years and 38 % of the 4-years survival (Fig. 3).

Because of abnormal character of analyzed data distributions, correlations between the age of patients, the hemoglobin level measured at a beginning, middle, and end of the treatment and the tumor and nodes regression assessed during following examinations were assessed using the non-parametric Spearman test. The only statistically significant correlation was found between the hemoglobin level at the beginning of the treatment and the degree of nodal regressions two months after the radiotherapy completion (R=–0.57, p=0.01). The regression scale had inverse values for their degrees, so the obtained result means that the nodal regression increases with the level of hemoglobin.

Analysis of the logit regression showed a statistically significant dependency between the primary tumor diameter and the probability of its local control (p=0.047) (Fig. 4).

No more dependencies between tumor and nodes dimension and probability of their control were found.

The proportional hazard Cox model showed significant impact on overall survival of involved lymph nodes diameter (p=0.004), the performance status (p=0.02) and the hemoglobin level at the beginning of treatment (p=0.04).

Discussion

Up to now, no one clinical trial has clearly showed a big therapeutic gain from altered radiotherapy of advanced head and neck cancer patients.

Interpretation of the obtained results is difficult because of the character of the analyzed group – the pilot group of a clinical trial whose lack of randomization makes rendering a proper conclusion difficult. There were a number of additional problems with respect to analyses: lengthy patient recruitment time (3.5 years) and a related large diversity of follow up periods, the small number of patients analyzed due to the decreasing percentage of patients in ad-

vanced disease stages and, frequently, a refusal to participate in the second phase of the trial, namely the evaluation of treatment toxicity only. The final appropriate conclusions concerning the survival of such irradiated patients might be formed after the third, last, randomized phase of study.

Of significant influence on the trial design was the data published in 1988 by WANG regarding twice daily irradiation with a fraction dose of 1.6 Gy up to 64 Gy with a 14-day gap in the middle. In the group of patients irradiated with this schedule, the 3 years actuarial survival was 85 % [19]. Decreasing the overall treatment time to 28 days, the possibility of locoregional control should growth up because of avoidance of tumor clonogen rapid repopulation [20].

The literature regarding altered fractionation in head and neck cancers is extensive. Unconventional fractionation, together with quality beam assurance, radiochemotherapy, radiosensitizers, and charged particle beam therapy, seems to be leading the way to improved treatment results. As was mentioned in the introduction, the main problem is the patient group with locoregionally advanced, inoperable lesions. One of the first attempts to improve radiotherapy results for advanced head and neck cancers was the schedule proposed in 1985 by NGUYEN et al [13]. The authors presented results of very aggressive hyperfractionation (8 daily fractions of 0.9 Gy up to 72 Gy in 10 days, delivered in two courses of 40 and 32 Gy, separated by a gap of two weeks). 68 % of patients had a complete remission at the end of the treatment, but 56 % of them relapsed. 34 % of patients had severe acute effects and 80 % heavy late sequelas; such a high percentage of severe toxicity necessitated a decrease in treatment intensity. Two years later, MARCIAL et al [12] published results of the hyperfractionated radiotherapy of advanced head and neck cancers (1.2 Gy twice a day up to 60 Gy). No gain was found as compared to conventional irradiation, with a higher incidence of acute and a similar level of late toxicity. Results of these two trials suggested that the incidence of acute and late toxicity depends not only on the fraction and the total dose but also on the intensity of irradiation. Taking it into account we have tried to design the irradiation scheme with the irradiation intensity lower than in the NGUYEN trial [13] but higher (a bigger fraction dose) than in the RTOG study [12].

Better results were reported after the hyperfractionated radiotherapy of head and neck cancer patients (1.8 Gy thrice a day, given by the 4 treatment days per week up to 59 Gy) [9]. The 3 years locoregional remission was 47 %, which is comparable to our results. We suspected that an improvement of

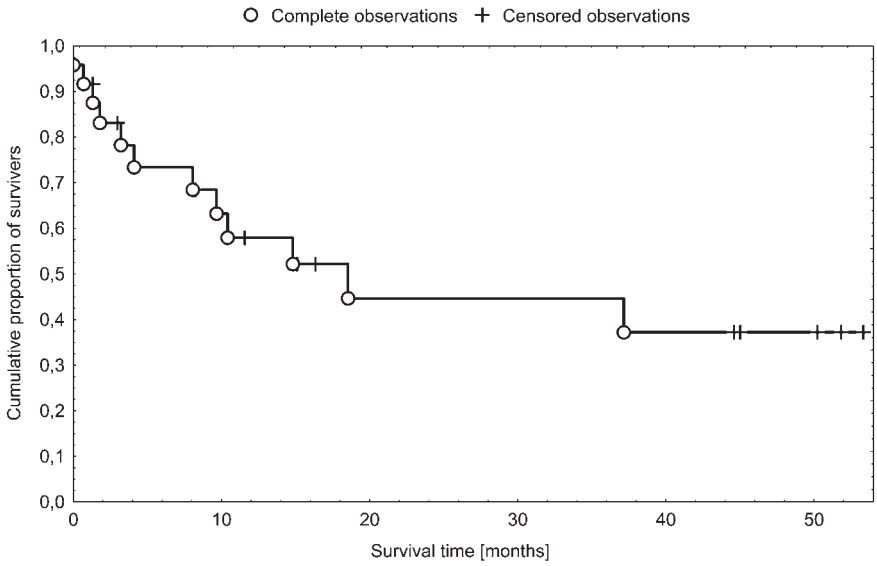

Figure 3. The survival analysis excluding deaths from distant metastases.

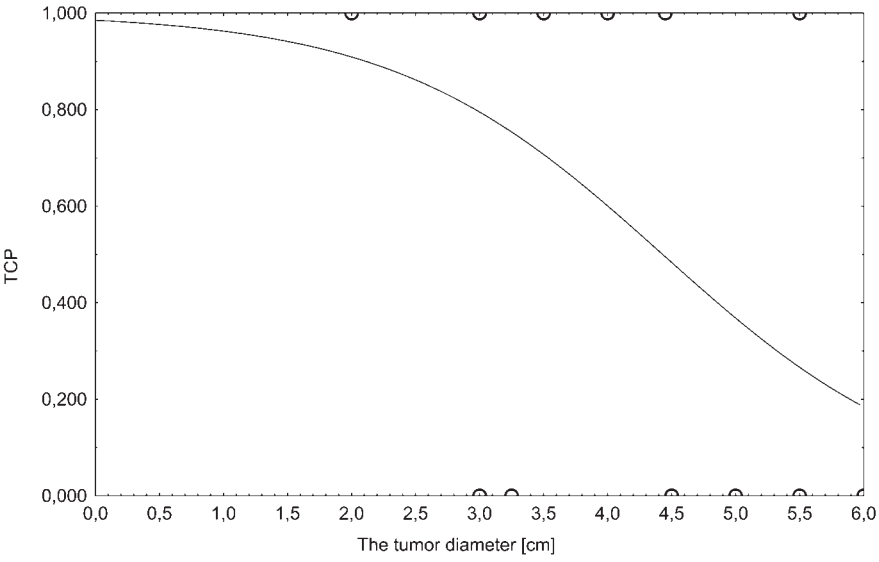

Figure 4. The logit regression analysis of dependency between the primary tumor diameter and the probability of its local control.

this result is possible, avoiding multiple and early (before 28 day of the treatment) gaps and increasing a total dose, so the result of the randomized phase of the CHA-CHA trial could be slightly better.

In a fashion similar to the RTOG study [12], patients were irradiated (1.2 Gy twice a day up to 67.2–76.8 Gy) in the trial published by COX et al [2]. No significant differences in survival were found, which confirms the thesis that 2.4 Gy per day in two fractions is not a sufficiently intensive irradiation and that a dose escalation with an overall treatment time prolongation does not improve results, probably due to an accelerated repopulation of tumor clonogens [20].

Similar results were reported by OLMI et al [14] after delivering 48–52 Gy in 11–12 days in 2 Gy fraction doses. The actuarial 5 years survival varied from 18 % for an advanced oral cavity to 38 % for an oropharynx cancer, and the late sequelas incidence was 28 %.

The RTOG 88-09 trial showed a lack of difference between the concomitant boost and the hyperfractionation 1.6 Gy twice a day, 5 times a week up to 67.2 Gy with a 2 week gap in the middle [4], which supports our opinion concerning insufficient irradiation intensity. In both arms the 2 years survival was 50 % [4].

Poor results of altered fractionation in advanced head and neck cancers had an impact on the seeking of chemotherapy support in addition to the unconventional irradiation. The report of PLASSIWILM et al [17] showed 80 % complete regression after chemoradiotherapy (Taxol + 72 Gy of the split course accelerated radiotherapy [9 days gap after 30 Gy]).

The superiority of an accelerated fractionation above the conventional one was presented by the EORTC 28851 trial (72.4 Gy in 45 fraction during 5 weeks) [7].

In the majority of the described regimens, the total doses were delivered during a period longer than 4 weeks, which allowed for an accelerated tumor cells repopulation. In some very intensive fractionation schemes [13, 14, 16] an incidence of sequelas was very high and thus unacceptable, so the concept of CHA-CHA trial provides hope that the survival rate will be relatively high and the percentage of late adverse effects low.

A comparison of the aforementioned treatment schemes' results is very difficult, not only because of different fraction and total doses and overall treatment times, but also – and perhaps mainly – because of the diversity in the cancer stage. In advanced head and neck cancers, and even for the same T and N group, differences can be huge. For example, T_4 of larynx cancer could be a small tumor infiltrating the thyroid cartilage or a large tumor involving a trachea, a hypopharynx, and/or neck soft tissues, so all precise comparisons should take into account detailed stratification according to tumor/node size.

On the basis of the obtained results we can conclude that the accelerated, hyperfractionated split course radiotherapy (CHA-CHA) could well be a valid method for advanced head and neck cancers treatment, but its true efficacy awaits confirmation in the next, randomized phase of trial.

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