Hyperfractionated Accelerated Radiotherapy versus Conventional Fractionation Both Combined with Chemotherapy in Patients with Locally Advanced Head and Neck Carcinomas

A Retrospective Analysis of a Monoinstitutional Series

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Key Words
Accelerated radiotherapy · Concomitant chemotherapy · 5-Fluorouracil · Head and neck cancer · Hyperfractionation · Mitomycin C

Abstract
Objective: Hyperfractionated accelerated radiotherapy (HART) has been combined with chemotherapy (CC) for locally advanced head and neck cancer, but no data from randomized trials are available for a comparison with conventionally fractionated radiotherapy (CFRT) and CC. ***Methods:*** This monoinstitutional retrospective study compares the results of both treatment schedules: 315 patients with locally advanced carcinoma (UICC stage III and IV) of the oral cavity and the orohypopharynx were treated from January 1990 to March 2006 with a radiochemotherapy combination based on mitomycin C and fluorouracil (HART-CC: 203 patients, CFRT-CC: 112 patients, total dose: 70–72 Gy) with curative intent. ***Results:*** Two- and 4-year survival was 60 and 42 (HART-CC) and 59 and 42% (CFRT-CC; p = 0.82, log-rank test), respectively. Using multivariate Cox regression, pretreatment hemoglobin level, N stage, tumor site but not the year of treatment, gender and T stage were significant prognosticators for survival. For locoregional control, only N stage was significant. The prognostic value of these pretreatment factors did not variate with the fractionation schedule used. ***Conclusions:*** In combination with CC, there was no trend towards an improved efficacy of HART in comparison with CFRT.

Introduction

Survival and locoregional control of locally advanced squamous cell carcinomas of the head and neck can be improved using hyperfractionated or accelerated radiotherapy (HART) in comparison to conventionally fractionated radiotherapy (CFRT) [1–15]. The increased efficacy has also been underscored by meta-analyses of randomized trials [16, 17].

Another successful way to increase the efficacy of definitive radiotherapy is concomitant chemotherapy (CC).

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Most data stem from trials using conventional fractionation concomitant with cisplatin-containing regimens [18].

In addition, mitomycin C (MMC)-containing CC schedules and radiotherapy have also been shown to improve survival or local control in comparison to radiotherapy alone [4, 19–23]. In one trial, improved local control was only found in the subgroup of N_0 patients [24]. Many randomized trials published in the last 10 years comparing the effects of concomitant radiochemotherapy versus radiotherapy alone used HART [4, 19, 25–29]. Therefore, a considerable amount of evidence for a therapeutic advantage of concomitant radiochemotherapy over radiotherapy alone has been derived from trials employing HART. On the other hand, HART schedules, giving a higher number of fractions with smaller than conventional doses per fraction up to the same total dose used in CFRT, represent a higher workload for the radiotherapy department especially when highly conformal radiotherapy delivery methods are used. Besides, these schedules may increase acute toxicity during treatment. In the absence of results from large randomized trials, the superiority of HART-CC over CFRT-CC remains to be proven at present. This monoinstitutional retrospective study was performed to compare treatment results of HART with those of CFRT, both combined with 5-fluorouracil (FU) and MMC, and to analyze prognostic pretreatment factors.

Patients and Methods

Patients

All patients of this retrospective comparison had squamous cell carcinomas of the oral cavity and the orohypopharynx at UICC stage III and IV. Two hundred and three patients of all 315 patients received HART-CC, the remaining 112 patients CFRT-CC.

Surgery prior to radiotherapy was confined to a biopsy. The initial staging procedures included a physical examination, panendoscopy, a computed tomography (CT) or a magnetic resonance imaging of the head and neck region, a CT of the chest or planar chest X-rays and an ultrasound examination or a CT of the abdomen.

HART-CC patients were treated between 1990 and December 2002, while CFRT-CC patients were treated between October 2000 and March 2006. The transit from HART-CC to CFRT-CC was undertaken in order to increase the number of patients that could be treated in the department per day and to decrease waiting times until the start of radiotherapy. This was done against the background that the benefit of HART-CC over CTRT-CC has never been proven.

Patients were scheduled for follow-up visits at the departments of head and neck surgery and radiotherapy at intervals $\leq$3 months during the first 2 years after treatment, $\leq$6 months up to the 5th year after treatment and annually thereafter. The date of death or confirmation of survival was obtained from the German residents' registration offices which were contacted in January 2007. The median follow-up period for the survival endpoint is 143 months for the HART-CC and 38 months for the CFRT-CC patients. The times to the endpoint locoregional control as the first site of recurrence were censored by the concurrent events distant metastases or secondary tumors, death or loss to follow-up.

Radiochemotherapy

The HART-CC schedule used hyperfractionated irradiation up to a total dose of 70.2–72 Gy in 6 weeks using 2 × 1.4 Gy per fraction and day in the last 3 weeks and simultaneous chemotherapy with MMC and 5-FU. The HART-CC schedule was given according to two variants with minor differences. According to the first variant, 72 Gy was given in 6 weeks: 2-Gy fractions/day for 5 days/week for 3 weeks followed by 2 × 1.4-Gy fractions/day for 5 days/week for the next 3 weeks, with an interval of at least 6 h between the two daily fractions. MMC was given at 10 mg/m^2 on day 5 (d5) and d36 after the start of radiotherapy (d1), 5-FU was given as a bolus at 350 mg/m^2 on d1 followed by continuous infusion at 350 mg/m^2/24 h (d1–d5). In addition, leucovorin was given as a 50 mg/m^2 bolus on day 1 followed by a continuous leucovorin infusion at 100 mg/m^2/24 h (d1–d5). One hundred patients were treated according to variant 1 from 1990–1994 [30]. Variant 2 consisted also of 2-Gy fractions/day for 5 days per week during the first 3 weeks followed by 2 × 1.4-Gy fractions/day for 5 days per week in the next 3 weeks up to a total dose of 70.2 Gy in 6 weeks (n = 103, treated from 1995–2003). The chemotherapy schedule of variant 2 was MMC at 10 mg/m^2 on d5 and d36, and 5-FU at 600 mg/m^2/day on d1–d5. Thus the 5-FU/leucovorin combination was substituted by 5-FU monotherapy at a higher dose as a decision of the Cooperative Clinical Trial Group in 1994 because of the preference of the majority of centers. The CFRT schedule used conventional fractionation, 2-Gy fractions/day for 5 days/week for 7 weeks up to a total dose of 70 Gy. MMC and 5-FU were given according to variant 2.

The radiotherapy technique has been described elsewhere [19]. The dose was prescribed and delivered according to the International Commission on Radiation Units and Measurement Report 50. Macroscopically, uninvolved neck node regions adjacent to the primary tumor or involved nodes received a total dose of 60 Gy and uninvolved nodes at low risk a total dose of 50 Gy, respectively. A salvage lymph node dissection was offered if residual suspect lymph nodes were detected at the first follow-up 6 weeks after radiotherapy completion. Written informed consent was obtained from all patients before the start of treatment.

Statistical Analysis

Endpoints of this analysis were death from any cause and locoregional failure as the first site of failure. In January 2007, the German residents' registration offices were contacted to obtain the most recent information on the vital status of all patients who missed a scheduled follow-up visit by >6 months. Data were obtained for all cases and used as the last follow-up information on death from any cause. The follow-up for observation of a locoregional recurrence was censored at the last scheduled follow-up visit which was attended by the patient. Survival curves and probabilities of locoregional recurrence over time were estimated according to the Kaplan-Meier method and compared with the log-

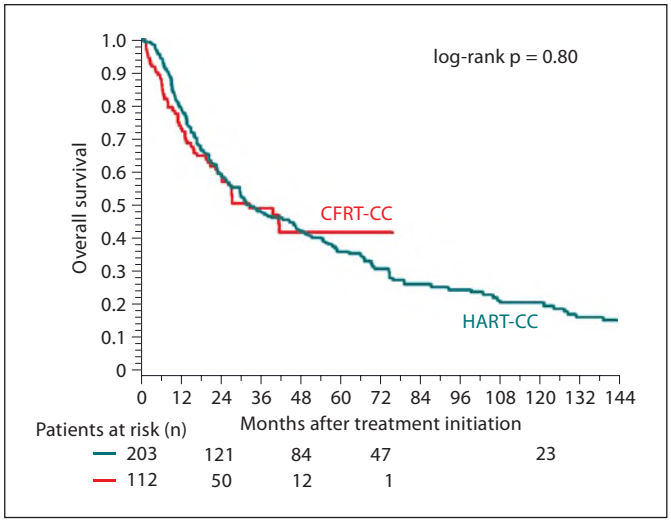

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Fig. 1. Overall survival according to the fractionation schedule.

rank test [31]. In addition, multivariate analysis was performed to assess the prognostic association of the pretreatment factors gender, age at diagnosis, T and N stages, the year of treatment, and the pretreatment hemoglobin concentration using the 25% quartile for men and women, i.e. 13 and 12 g/dl, as a cutoff point. In addition, the effect of the fractionation schedule, i.e. HART or CFRT, on outcome was analyzed using multivariate Cox regression to adjust for significant pretreatment prognostic factors [31].

Results

Patient Characteristics

Pretreatment characteristics of the patients are given in table 1. The HART-CC and CFRT-CC groups did not differ except for a higher proportion of oral cavity carcinomas ($p = 0.001$, χ^2 test) in HART-CC patients.

Survival

There were no differences in survival between HART-CC and CFRT-CC patients (fig. 1). Survival rates at 2 and 4 years were 60 and 42% after HART, respectively, and 59 and 42% after CFRT, respectively ($p = 0.82$, log-rank test). The hazard ratio (HR) of death in the HART-CC group versus the CFRT-CC group was 0.96 (0.70–1.33) in the univariate Cox model. Using multivariate Cox regression, prognostic pretreatment factors were analyzed. Starting with the full model including all pretreatment characteristics in table 1 (age, gender, pretherapeutic hemoglobin, tumor site, and T and N stages) as well as the year of treatment, a backward selection procedure was used. Only the N stage, hemoglobin and tumor site (hypopharynx vs. others) remained significant at the level of $\alpha = 0.05$ in multivariate analysis (table 2). Regarding tumor site, comparing oral cavity carcinomas with oropharyngeal carcinomas in addition to hypopharyngeal cancer did not become significant and was eliminated from the model by the backward procedure (HR of death: 0.82, range 0.42–1.60, $p = 0.56$). All those characteristics that became significant in multivariate analysis were also significant in univariate analysis using the log-rank test (table 3). The reason for the lower survival in patients with hypopharyngeal carcinomas was a higher rate of distant

Table 1. Characteristics of the patients

Characteristics	HART-CC (n = 203)	CFRT-CC (n = 112)
Median age, years	54	60
Gender, %		
Male	81	72
Female	19	28
Pretherapeutic hemoglobin, %		
<12 (f) or <13 g/dl (m)	22	26
≥12 (f) or ≥13 g/dl (m)	78	64
Tumor site, %		
Oropharynx	54	44
Hypopharynx	42	40
Oral cavity	4	16
TNM stage, %		
T_1	2	4
T_2	9	18
T_3	28	25
T_4	60	52
T_x	1	1
N_0	15	9
N_1	15	7
N_2	62	75
N_3	6	8
N_x	2	1
M_0	100	100
UICC stage, %		
III	11	5
IV	86	93
Salvage neck dissection, %	20.2	19.8
Prophylactic PEG before RT, n/total n	17/203 (8%)	15/112 (13%)
PEG required during RT, n/total n	27/186 (15%)	19/97 (20%)
Parenteral nutrition during RT, n/total n	57/186 (31%)	19/97 (20%)
Mean weight loss, %	6.1	5.3

f = Females; m = males; RT = radiotherapy.

Table 2. Results of multivariate Cox analysis

	Death			Locoregional relapse		
	HR	95 CI	p value	HR	95 CI	p value
N category			0.0001			0.009
N_0 vs. N_2	0.55	0.34–0.87	0.01	0.32	0.14–0.74	0.008
N_1 vs. N_2	0.63	0.41–0.98	0.04	0.60	0.32–1.14	0.12
N_3 vs. N_2	2.44	1.47–4.07	0.0006	1.70	0.81–3.56	0.16
Hemoglobin						
Low vs. normal	1.44	1.05–1.98	0.02			
Site						
Hypopharynx vs. other	1.34	1.02–1.78	0.04			
Treatment schedule						
HART vs. CFRT	1.15	0.82–1.62	0.41	1.12	0.71–1.77	0.63

Significant patient-dependent covariates in addition to the fractionation effect according to the Cox-regression model. A backward selection procedure was used starting with the full model that included age, gender, tumor stage, N category, site of the primary tumor and pretherapeutic hemoglobin level and the fractionation effect which remained in the model. Low (high) hemoglobin = Pretherapeutic level <12 g/dl (≥12 g/dl) for females or <13 g/dl (≥13 g/dl) for males; CI = confidence interval.

Table 3. Results of univariate Kaplan-Meier analysis

	Survival			Locoregional relapse		
	2-year survival	95 CI	p value	2-year relapse	95 CI	p value
N category			0.0001			0.006
N_0	0.75	0.62–0.89		0.14	0.03–0.26	
N_1	0.77	0.63–0.90		0.21	0.07–0.35	
N_2	0.57	0.50–0.64		0.38	0.30–0.46	
N_3	0.24	0.05–0.43		0.54	0.25–0.82	
Hemoglobin						
Low	0.50	0.38–0.62	0.004			
Normal	0.62	0.55–0.68				
Site			0.04			
Hypopharynx	0.54	0.46–0.63				
Other	0.63	0.56–0.70				
Treatment schedule			0.8			0.94
HART-CC	0.60	0.53–0.67		0.33	0.26–0.40	
CFRT-CC	0.59	0.49–0.67		0.34	0.23–0.46	

Kaplan-Meier estimates of 2-year survival by the different pretreatment variables. p values were obtained by log-rank test. Low (high) hemoglobin = Pretherapeutic levels <12 g/dl (≥12 g/dl) for females or <13 g/dl (≥13 g/dl) for males; CI = confidence interval.

metastases (17% at 2 years vs. 11% for patients with tumors at other sites; p = 0.03, log-rank test). The survival of patients with cancers of the oropharynx and oral cavity at 2 years was 0.63 (0.55–0.71) and 0.65 (0.47–0.84), respectively. The effect of the fractionation schedule on survival was also analyzed using the multivariate Cox model to adjust for all pretreatment factors. The risk of death was similar in the HART-CC and CFRT-CC groups (HR: 1.15 HART-CC/CFRT-CC; range 0.82–1.62, p = 0.41). In addition, survival did not differ between vari-

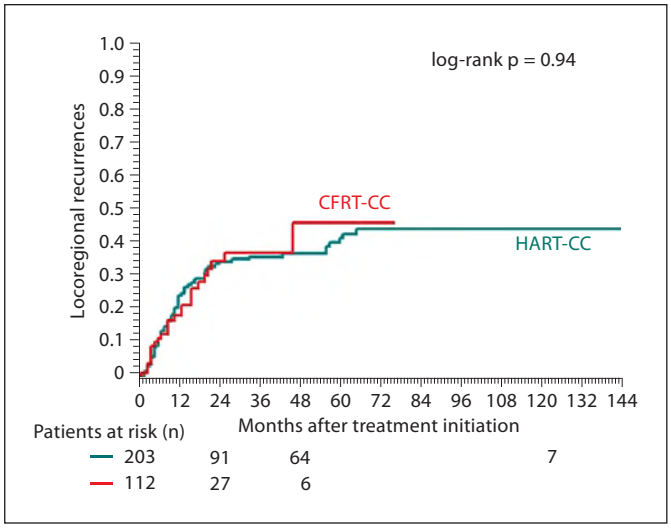

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Fig. 2. Locoregional recurrences according to the fractionation schedule.

ants 1 and 2 of the HART-CC schedule in univariate analysis (HR: 0.91; range 0.65–1.15, p = 0.56). The prognostic value of pretreatment characteristics did not vary with the type of fractionation, i.e. HART-CC versus CFRT-CC ($p > 0.2$, χ^2 test).

Locoregional Control

The probabilities of locoregional relapse according to the Kaplan-Meier method were similar for HART-CC and CFRT-CC patients (fig. 2), being 33% for HART-CC and 34% for CFRT-CC patients at 2 years (p = 0.94, log-rank test). The HR for locoregional relapse of HART-CC/CFRT-CC was 0.98 (0.63–1.54), respectively, according to univariate Cox analysis. Using multivariate Cox regression with backward elimination, only N stage remained significant (table 2). The hemoglobin level was eliminated at an HR of 1.10 (0.67–1.81) for low hemoglobin in comparison to normal hemoglobin. The HR for locoregional relapse of HART-CC versus CFRT-CC patients was 1.12 (0.71–1.77) using the multivariate Cox model adjusting for N stage.

Toxicity of Treatment Schedules

The need of percutaneous endoscopic gastrostomy (PEG) or full parenteral nutrition for at least 2 days during the course of radiochemotherapy was used as a criterion for grade III dysphagia due to mucositis of the upper aerodigestive tract according to the Common Terminology Criteria for Adverse Events (version 3.0) [32]. Some patients with low performance status received a prophylactic PEG before the start of radiotherapy, but the percentages of those patients did not significantly differ between the HART-CC and CFRT-CC schedules (table 1, p = 0.16, χ^2 test). In addition, the proportion of patients without a PEG at the start of radiotherapy that required a PEG or full parenteral nutrition during therapy did not differ between the treatment groups with 45 and 39% for the HART-CC and CFRT-CC schedules, respectively (p = 0.34, χ^2 test). In addition, the percentage of weight loss was similar in both treatment groups, with mean values of 6.1 and 5.3% in the HART-CC and CFRT-CC groups, respectively (p = 0.44, Wilcoxon test). Therefore, severe acute side effects were similar as assessed by these robust criteria.

Discussion

Acceleration without dose reduction and hyperfractionation are modifications of definitive radiotherapy in locally advanced head and neck carcinomas which can improve locoregional control in comparison to conventional fractionation according to the meta-analysis of Bourhis et al. [1]. The HART schedule used in the present study can be classified as an accelerated fractionation schedule without total dose reduction according to the criteria of the aforementioned meta-analysis. Overall treatment time was shortened by 1 week, occurring in five of the eight trials grouped under acceleration without total dose reduction in the meta-analysis above. Using radiotherapy alone, the results from this meta-analysis show that such an acceleration schedule will reduce the probability of locoregional recurrences in comparison to CFRT with an HR of 0.79 (0.72–0.87), but will not reduce the HR of death (HR 0.97, range 0.89–1.05). Assuming that the effects of chemotherapy and intensification of radiotherapy are independent, an improvement in locoregional control but not in survival can be expected from HART in comparison to CFRT in the present study using additional CC. In accordance, the HR of death using multivariate analysis and adjusting for prognostic pretreatment factors was 1.15 (0.82–1.62) and therefore showed no benefit of HART-CC compared with CFRT-CC. However, the risk of locoregional recurrence was even larger in the HART-CC group than in the CFRT-CC group, characterized by an HR of 1.12 (0.71–1.77). Therefore, we did not find a benefit of HART-CC with moderately accelerated fractionation and MMC/5-FU over CFRT-CC regarding the endpoint locoregional control

in this large retrospective study. Although this retrospective analysis of a monoinstitutional series is not able to substitute a randomized trial, it provides estimates of the HR for locoregional control and survival in the absence of results from randomized trials, possibly implying that HART using CC with MMC and 5-FU is not superior to CFRT. In the absence of a proven therapeutic gain, there are some caveats on HART-CC because of the increased acute toxicity and the higher workload [5, 6, 11, 12]. The former may limit the dose intensity of novel CC regimens. However, acute toxicity was not higher in our patients treated with HART-CC compared with CFRT-CC regarding the need for PEG or full parenteral nutrition during therapy. In addition, weight loss was similar at the end of both schedules. RTOG 0129 [33] will be another critical trial on concomitant radiochemotherapy comparing acceleration without dose reduction in comparison to conventional fractionation. In that study, CC consisted of cisplatin. The study has been closed to patient accrual with more than 700 patients entered, but survival data have not yet been presented.

Repopulation and hypoxia are resistance mechanisms for CFRT whose importance might be altered by both HART [34] and CC. Targeting the same resistance mechanisms, however, may not lead to additional effects. MMC inhibited repopulation of xenografted human squamous cell carcinomas during fractionated radiotherapy [35]. In addition, MMC, a bioreductive alkylating agent, was found to target hypoxic cells in a selective manner [36]. While hemoglobin was a general prognostic factor for survival in this study, we did not find an effect of the hemoglobin level on locoregional recurrences, being in line with results from other studies on hypoxic modifiers such as oxygen and nicotinamide [37] or MMC [38] that also did not find an effect of the pretreatment hemoglobin level on locoregional recurrences, pointing to the effectiveness of such drugs on hypoxic tumor cell populations. On the other hand, in studies using platinum-containing CC, the risk of locoregional recurrences was not increased in patients with low hemoglobin levels [28, 39, 40]. Here, hemoglobin levels of 12 and 13 g/dl were used as cutoff levels for females and males for normal and low hemoglobin, which coincide with the lower quartiles of the respective pretreatment hemoglobin levels. It is known that below these levels tumor oxygenation worsens [41].

In conclusion, the present long-term follow-up study did not demonstrate an advantage of HART-CC over CFRT-CC. N stage was the strongest prognostic factor for local control and survival.

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