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Original article

Combined concomitant boost radiotherapy and chemotherapy in stage III–IV head and neck carcinomas: A comparison of toxicity and treatment results with those observed after radiotherapy alone

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Summary

Background: Alteration of radiation therapy (RT) fractionation and the combination of chemotherapy (CT) with RT represent two predominant fields of current research in the treatment of head and neck carcinomas. To assess the potential integration of these two fields, a retrospective comparison of toxicity and treatment outcome was carried out in stage III–IV patients treated with a concomitant boost RT schedule with or without CT.

Patients and methods: Fifty-two patients were treated by RT alone and 35 by RT and CT. In the RT group, there were significantly fewer T3–4 tumors (56% vs. 88%, $P = 0.002$) and higher proportion of planned neck dissections (35% vs. 14%, $P = 0.047$). The planned total dose was 69.9 Gy delivered over 5.5 weeks. In 10 cases CT was given before RT and in 25 concomitantly with RT, either alone or with neoadjuvant and/or adjuvant CT. All patients but two had cisplatin-based (CDDP, 100 mg/m^2) CT, associated in 28 patients with 5-fluorouracil (5-FU, 1000 mg/m^2/24 h × 5). The median follow-up for the surviving patients was 21 and 31 months for the RT and RT–CT groups respectively.

Results: Grade 3–4 acute toxicity (RTOG) was observed in 73% and 86% of patients, and grade 3 dysphagia in 31% and 57% ($P = 0.02$) respectively in the RT and RT–CT groups. The rates of grade 3–4 late complications were similar in the two groups (5% vs. 12%). At three years, actuarial loco-regional control (LRC) was 57% and 66% ($P = 0.66$) and overall survival was 56% and 47% ($P = 0.99$) in the RT and RT–CT groups respectively.

Conclusions: While acute toxicity was higher compared with RT alone, this accelerated RT schedule was feasible in association with 5-FU/CDDP, even administered concomitantly. Despite the significant proportion of more advanced disease in the RT–CT group, LRC was similar to that obtained by RT alone. Combinations of concomitant boost RT and chemotherapy merit further investigation in prospective trials.

Key words: accelerated radiotherapy, chemotherapy, head and neck cancer

Introduction

The prognosis of patients with advanced head and neck carcinomas treated by standard radiation therapy (RT) is generally very unfavorable [1–3]. Both the use of unconventional fractionation schedules and the adjunction of chemotherapy to RT are undergoing investigation in the hope of improving these unsatisfactory results [4–17]. The encouraging initial results of the concomitant boost technique [9, 18] led in 1991 to the introduction at the University Hospital of Geneva of a modified concomitant boost schedule in which the boost to the clinically involved sites was delivered in a progressively accelerated fashion during the last 3.5 weeks of a 5.5 week treatment course. For stage III–IV disease, chemotherapy was initially added sequentially prior to RT and then progressively more frequently in a concomitant fashion. In order to establish whether or not a concomitant boost schedule is compatible with the simultaneous administration of chemotherapy, the therapeutic outcome and toxicity of the combined treatment have been retrospectively analyzed and compared with those obtained in a group of patients treated during the same period with the identical RT regimen but without chemotherapy.

Patients and methods

Patients

From January 1991 to October 1995, 87 patients with resectable or unresectable stage III–IV head and neck carcinomas were treated with concomitant boost RT, of whom 35 (40%) received combined chemo-radiotherapy. Compared with patients treated with radiotherapy alone (RT group), those receiving chemotherapy (RT–CT group) tended to have bulkier disease. The characteristics of the two groups of patients are given in Table 1.

Radiation therapy

The treatment schedule planned to deliver a total dose of 69.9 Gy in 41 fractions over a period of 38 days. The basic course, including all involved sites and areas of potential microscopic disease (generally the primary tumor area and both sides of the neck down to the clavicles), was given in daily fractions of 1.8 Gy, five times a week to a total dose

Table 1. Patient characteristics.

	RT group (52 patients)	RT–CT group (35 patients)	*P*
Mean age (standard deviations)	61 years (11)	54 years (16)	0.04
Gender: male/female	39/13	24/11	
WHO performance status			
0–1	36 (72%)	31 (89%)	0.1
2–3	14 (28%)	4 (11%)	
Tumor location			
Oral cavity + oropharynx	27 (52%)	21 (60%)	
Hypopharynx + larynx	19 (36%)	9 (26%)	
Nasopharynx	6 (12%)	5 (14%)	
TN stage			
T1–2	23 (44%)	4 (12%)	0.002
T3–4	29 (56%)	31 (88%)	
NO	11 (21%)	8 (23%)	
N1–3	41 (79%)	27 (77%)	
AJCC stage			
III	18 (35%)	7 (20%)	0.15
IV	34 (65%)	28 (80%)	

of 50.4 Gy over 5.5 weeks. The boost to initial sites of macroscopic tumor involvement consisted of 13 fractions of 1.5 Gy (19.5 Gy) and was given as a second daily fraction, starting the last day of the second week of the basic treatment, in a progressively accelerated fashion (Figure 1). The minimum interval between the two daily fractions was six hours.

The larger volume was treated generally with two opposed laterals and one anterior field, using 6 MV photon beams in most patients. The field arrangement for the boost was individualized according to the tumor extent and location. The cervical spinal cord was blocked at a dose of 45 Gy or less, and irradiation of the posterior neck was then continued with electrons of appropriate energy. The supraclavicular lymph nodes generally received a dose of 45–50.4 Gy in 25–28 fractions. No specific technical modifications were used in the group of patients receiving chemotherapy.

Surgery

No patient received surgery to the primary tumor. Before RT, a uni- or bilateral neck dissection was performed in 18 patients in the RT group and five in the RT–CT group ($P = 0.047$), and two patients in the RT group had an adenectomy. Otherwise surgery was reserved for salvage of loco-regional failures.

Chemotherapy

In the initial patients chemotherapy was delivered sequentially prior to starting RT. Apparently satisfactory tolerance led to a gradual shift toward the administration of an increasing proportion of the chemotherapy concomitantly with RT. Thus in 10 cases chemotherapy was administered only prior to, and in 25 concomitantly with RT, either alone or with neoadjuvant and/or adjuvant chemotherapy.

Except for two patients treated with weekly carboplatin, all patients received cisplatin (CDDP), associated with 5-fluorouracil (5-FU) in 28 patients, with epirubicin + bleomycin in four patients, and administered alone in one patient. Twenty-two (63%) patients received three cycles, nine (26%) two cycles, and two (6%) one cycle. In patients receiving at least part of their chemotherapy concomitantly with RT, chemotherapy consisted of CDDP and 5-FU in 21 patients (84%). Fourteen patients received one cycle, and seven patients two cycles, administered generally on the first and the fourth week of RT. CDDP (100 mg/m^2) was given as a rapid intravenous infusion followed by continuous 24-hour intravenous infusion of 5-FU (1000 mg/m^2) for five days. During RT, the dose of 5-FU was reduced by 20%–40% in the second course, according to the severity of the acute mucosal reactions.

Table 2. Acute morbidities in the two groups of patients.

	RT group (52 patients)	RT–CT group (35 patients)	*P*
Overall grade 3–4	38 (73%)	30 (86%)	0.2
Grade 3–4 mucositis	34 (65%)	24 (69%)	1
Grade 3 dysphagia	16 (31%)	20 (57%)	0.02
Hospitalisation	9 (17%)	14 (40%)	0.02
Median duration (range)	12 days (4–150)	19 days (11–150)	
Nasogastric tube or gastronomy	13 (25%)	18 (51%)	0.02
Median duration (range)	38 days (4–150)	38 days (11–150)	
Median weight loss during radiotherapy (range)	4.6 kg (0–14)	4 kg (0–11)	

Statistical methods

The actuarial overall and disease-free survival rates as well as actuarial local and loco-regional control rates were calculated by using the Kaplan–Meier method [19]. The Fisher's exact test, the unpaired *t*-test, and the logrank test were used to assess for significant differences between simple proportions, means, and survival curves respectively.

Results

All the patients completed the planned irradiation schedule except one in the RT–CT group. All three treatment interruptions due to acute toxicity occurred in the RT–CT group (split duration 5, 17, and 35 days). The median overall treatment time was 41 days (range 36–50 days) for the RT group and 39 days (range 37–79) for the RT–CT group. The median tumor dose for both groups was similar (69.9 Gy, range 62.5–72.9).

Morbidity

According to the RTOG grading system [20], all acute reactions were grade 2 or more. The majority were grade 3 reactions, with only one patient in the RT group and two patients in the RT–CT group presenting with grade 4 acute toxicity. The main acute toxicity parameters for the two groups are displayed in Table 2. In the RT–CT group, grade 3 dysphagia was more frequent with concomitant (64%) than with neoadjuvant (45%) chemotherapy administration.

According to the World Health Organization (WHO) grading system [21], 12 patients (36%) in the RT–CT group presented with grade 3–4 hematological complications. Grade 3 gastrointestinal complications were observed in four patients, and grade 3 skin reactions in one patient. Three patients presented with a vascular thrombosis requiring anticoagulation, three with alopecia and one with hearing impairment.

Week	1	2	3	4	5	6
Wide fields (50.4 Gy/28 fr.)	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXX
Boost (19.5 Gy/13 fr.)	_____	____X	X___X	X_X_X	X_XXX	XXX

Figure 1. Schematic representation of the radiotherapy protocol.

Three patients in the RT group and one in the RT–CT group died during the three months following radiotherapy of causes not clearly related to tumor progression. One patient, who refused supportive care, died of malnutrition; one malnourished patient died from candida septicemia; one patient died from pneumonia as a consequence of severe laryngeal edema; and one patient died from a massive oropharyngeal hemorrhage in a setting of post-chemotherapy thrombopenia.

Seventy-three patients were evaluable for long-term complications (patients with a minimum follow-up of three months and with available data). Most complications were RTOG grade 2 (52% and 42% in the RT and RT–CT groups, respectively). Grade 3–4 complications were observed in 5% and 12% in the RT and RT–CT groups, respectively ($P = 0.4$).

Clinical outcome

At last follow-up, 31 patients in the RT group and 17 in the RT–CT group were still alive, and one patient in each group was lost to follow-up (14 and 11 months). In patients having died, head and neck cancer was considered the cause of death in 14 of 20 patients in the RT group and 11 of 17 patients in the RT–CT group. The median follow-up for the surviving patients was 21 months (range 2–60) and 31 months (range 4–54) for the RT and RT–CT groups, respectively.

Local and locoregional control rates were estimated for patients with a minimum follow-up of one year and without taking into account the contribution of salvage surgery. At three years actuarial local control was 70% in the two groups and actuarial loco-regional control was 57% and 66% for the RT and RT–CT groups, respectively ($P = 0.66$). The three-year actuarial overall survival was 56% and 47% ($P = 0.99$), and the three-year disease-free survival was 53% and 60% for the RT and the RT–CT groups, respectively ($P = 0.8$).

Discussion

Unconventional radiation fractionation schedules and the association of chemotherapy with RT represent the main innovative approaches currently under study for the treatment of unfavorable head and neck cancers. Progress in this area has been impeded by the problem of unacceptable acute toxicity, and various strategies have been developed to assure the feasibility of these aggressive treatment programs. In the case of accelerated RT schedules, tolerance has been variously improved by reducing the total dose (very accelerated continuous course), interposing a treatment gap (accelerated split course), or reducing the volume submitted to accelerated fractionation (concomitant boost). On the other hand, for combinations of chemo- and radiotherapy, many investigators have preferred sequential or alternating schedules, in order to avoid the toxicity associated with the concomitant administration of the two modalities. Moreover, chemotherapy has often been limited to single agents, and RT administered using standard fractionation or using split course techniques. In contrast, the feasibility of concomitant chemotherapy and continuous accelerated RT has not been extensively investigated.

There is increasing evidence that locoregional control can be improved through the use of various hyperfractionated and accelerated RT programs [1, 4, 6, 9, 22]. Considering the logistical convenience and the encouraging initial results of concomitant boost schedules [9], a modified concomitant boost program was developed, in which the 13 second daily fractions were given in a progressively accelerated manner starting on day 12 of the basic treatment. This schedule design was based on the notion, as suggested by both experimental and clinical data [23, 24], that cancer clonogen repopulation may become significant as early as two weeks after initiation of RT, and that the incremental dose required to compensate for tumor proliferation might increase progressively toward the end of treatment.

At the same time, and with the aim of increasing the efficacy of this accelerated RT schedule, selected patients with very advanced disease were given chemotherapy. Initially chemotherapy was given sequentially before RT, but since this mode of administration had come under serious criticism [8, 11, 25], a decision was made to give at least part of the chemotherapy concomitantly with irradiation. The choice of 5-FU/CDDP was motivated by the reported activity of this combination in head and neck cancers [3, 12] and by the radiosensitizing properties attributed to CDDP [26, 27].

As expected from any accelerated RT program, the rate of grade 3–4 acute reactions was high and was increased by the adjunction of chemotherapy (Table 2). Indeed, compared with the RT group, there was greater overall acute toxicity and significantly more grade 3 dysphagia in the RT–CT group, and patients receiving combined treatment more frequently required hospitalization and needed significantly more nutritional support. However, it is the authors' impression that acute toxicities were equally manageable in the two groups, particularly when timely supportive care was provided. The most significant therapeutic disadvantage of combined treatment was the occasional disruption of RT delivery.

In this retrospective analysis, locoregional control, disease-free survival, and overall survival were not significantly different between the two groups. This appears to be in contradiction to the results of some randomized studies comparing concomitant chemoradiotherapy with RT alone, which demonstrate significantly better loco-

regional control [14–16], and suggest a statistically significant improvement in survival with combined treatment [28, 29]. However, as a result of patient selection, the composition of the two groups in the present study was not at all similar (Table 1). In particular, in the RT–CT group there were fewer patients having had neck dissections and a higher percentage of T3–T4 tumors. It is thus impossible to draw conclusions from the current study regarding the potential benefits of the combined treatment.

In the absence of randomized comparisons the choice of RT regimen for treating unfavorable head and neck cancers will be determined by convenience, toxicity profile, and the feasibility of administration simultaneously with effective antitumor agents. Although highly accelerated continuous regimens are likely to be incompatible with such combined therapy, our initial clinical results suggest that the concomitant boost program described in the present paper can be administered together with standard combination chemotherapy with acceptable toxicity. The locoregional control obtained in the present series of patients with stage III–IV disease is encouraging. A confirmation of these results in prospective studies appears justified.

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