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ALLAL, Abdelkarim Said, *et al*.

Abstract

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Reference

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CLINICAL INVESTIGATION **Head and Neck**

CAN CONCOMITANT-BOOST ACCELERATED RADIOTHERAPY BE ADOPTED AS ROUTINE TREATMENT FOR HEAD-AND-NECK CANCERS? A 10-YEAR SINGLE-INSTITUTION EXPERIENCE

ABDELKARIM S. ALLAL, M.D.,* DANIEL TAUSSKY, M.D.,* NICOLAS MACH, M.D.,† MINERVA BECKER, M.D.,‡ SABINE BIERI, M.D.,* AND PAVEL DULGUEROV, M.D.§

*Division of Radiation Oncology, University Hospital of Geneva, Geneva, Switzerland; †Division of Medical Oncology, University Hospital of Geneva, Geneva, Switzerland; ‡Division of Diagnostic Radiology, University Hospital of Geneva, Geneva, Switzerland; §Division of Head and Neck Surgery, University Hospital of Geneva, Geneva, Switzerland

Purpose: Accelerated schedules are effective in overcoming repopulation during radiotherapy (RT) for head-and-neck cancers, but their feasibility is compromised by increased toxicity. The therapeutic ratio may be particularly favorable for 5-week regimens. This study reports the 10-year experience of a single institution in the routine use of concomitant boost RT as standard radical treatment in all but the most favorable stage patients.

Methods and Materials: Between February 1991 and June 2001, 296 patients (mean age, 59 years) were treated with concomitant boost RT either alone (67%) or combined with cisplatin-based chemotherapy (33%), with a median tumor dose of 69.9 Gy. Tumors were located in the oropharynx in 52%, hypopharynx in 20%, larynx in 15%, nasopharynx in 7%, and oral cavity in 6%. International Union Against Cancer Stage III-IV disease represented 77% of tumors. The median follow-up for surviving patients was 55 months (range, 10–138 months).

Results: The RT schedule was completed to the prescribed dose in all but 1 patient. Twenty patients (7%) had a treatment interruption (median, 5 days; range, 2–35 days). Grade 3-4 Radiation Therapy Oncology Group acute toxicity was observed in 77% of patients, and nutritional support was required in 110 patients (37%). For all patients, the 5-year actuarial locoregional control and disease-free survival rate was 72% and 61%, respectively. In a multivariate analysis, only T and N stage was significantly associated with locoregional control and disease-free survival. Grade 3-4 late toxicity occurred in 14%, mostly bone and cartilage necrosis.

Conclusions: The present, moderately accelerated, concomitant boost regimen is logistically feasible, causing minimal inconvenience to the technical staff and yielding a high rate of patient compliance. Concomitant chemotherapy administration is feasible provided that patients are carefully selected and supportive care is introduced in a timely fashion. Considering the manageable toxicity and the satisfactory tumor control obtained, this regimen represents a good choice when considering implementation of an altered RT fractionation schedule as standard treatment for head-and-neck cancers. **© 2004 Elsevier Inc.**

Head-and-neck cancer, Accelerated radiotherapy, Chemotherapy.

INTRODUCTION

Accelerated fractionation regimens were initially developed to reduce the impact of tumor repopulation as a major cause of treatment failure in head-and-neck cancer (1–3). The recent, large, randomized Radiation Therapy Oncology Group (RTOG) trial (4) demonstrated the superiority of both hyperfractionated radiotherapy (RT) and accelerated RT (concomitant boost) over standard RT fractionation in terms of locoregional control and disease-free survival, but at a cost of greater acute and late toxicity. Although the feasibility of accelerated RT schedules has been demonstrated in prospective studies in selected patients, routine use of such regimens is not yet established for the treatment of unselected patients, for whom monofractionated RT remains the standard of care in many institutions. The concomitant boost technique used in the RTOG trial (4) was first introduced by the M.D. Anderson Cancer Center (2, 5). On the basis of the encouraging results reported by the latter group, a similar concomitant boost RT schedule was introduced into routine practice in Geneva >10 years ago. Since 1991, essentially all patients treated with radical RT for head-and-neck carcinomas have been treated according to this schedule, with the exception of those enrolled in prospective trials or those presenting with very small tumor

Reprint requests to: Abdelkarim S. Allal, M.D., Division de Radio-oncologie, Hôpitaux Universitaires de Genève, 24 rue Micheli-du-Crest, Geneva 1211, Switzerland; Tel: (+41) 22-382-7124, ext. 090; Fax: (+41) 22-382-7117; E-mail: abdelkarim.alla1@hcuge.ch

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Table 1. Patient characteristics (n = 296)

Characteristic	Value
Age (y)	
Mean	59
Range	15–99
Gender (*n*)	
Male	230
Female	66
Performance status (WHO) (*n*)	
0/1	180/73
2/3	23/5
Unknown	15
Tumor histologic type (*n*)	
Squamous cell	288
Undifferentiated	8
Tumor differentiation (*n*)	
Well-moderate	182
Poor	71
Unknown	43
Tumor location (*n*)	
Oral cavity	18
Oropharynx	154
Hypopharynx	58
Larynx	45
Nasopharynx	21
T stage (UICC 1997)	
T1/T2	39/102
T3/T4	80/75
N stage	
N0/N1	120/44
N2/N3	118/14
UICC stage	
I	13
II	56
III	62
IV	165

Abbreviations: WHO = World Health Organization; UICC = Union Internationale Contre le Cancer.

volumes (e.g., T1 of the vocal cord). In this paper, we analyzed the overall feasibility, oncologic outcome, and early and late toxicity associated with this regimen in our experience, with a view toward the future directions to be developed on the basis of this experience.

METHODS AND MATERIALS

Patients

Between February 1991 and June 2001, 296 head-and-neck cancer patients were treated with accelerated RT using a concomitant boost technique. The pretreatment workup consisted of medical history and physical examination, chest X-ray, and CT and/or MRI of the head-and-neck region, as well as panendoscopy. For tumor classification, the International Union Against Cancer (UICC) staging system was used (1997). The pretreatment patient characteristics are displayed in Table 1.

Radiotherapy

The RT schedule has been described previously in detail (6). The planned total dose was 69.9 Gy, delivered in 41 fractions during a 38-day period. The basic course was given in daily fractions of 1.8 Gy, 5 times weekly to a total dose of 50.4 Gy within 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. The minimal interval between the two daily fractions was 6 hours. Most of patients were treated with two opposed lateral fields and one anterior field for the large volume; for the boost, an individualized technique was used according to the tumor location and extent. Most patients were treated with 6-MV photon beams, and irradiation of the posterior neck was then continued with electrons of appropriate energy.

Surgery

According to our institutional policy, 39 patients (14%) underwent a planned neck dissection before RT; either radical (unilateral in 29 and bilateral in 2 patients) or modified radical (unilateral in 6, bilateral in 2 patients). Three additional patients underwent simple excisions of lymph node metastases. Otherwise, surgery was reserved for salvage of locoregional failure.

Chemotherapy

Chemotherapy was usually proposed for T3-4 or N2-3 tumors, provided that the patient's medical condition was judged fit enough to tolerate multimodality treatment. Ninety-seven patients (33%) received one or more cycles of chemotherapy, at least a portion of which was administered concomitantly with RT in 82 patients (85%). In 14 patients, chemotherapy was administered before, and in 1 patient after, RT. In 57 patients one to two cycles of chemotherapy were administered and in 40 patients three or more. Concomitant chemotherapy consisted of two cycles of cisplatin (80–100 mg/m^2 or 5 $\times$ 20 mg/m^2) either alone (24%) or combined (63%) with 5-fluorouracil (800–1000 mg/m^2, 96-h continuous infusion), usually during the first and fifth week of RT. The remaining patients, mainly presenting with nasopharyngeal carcinomas, received different drugs such as bleomycin and epirubicin.

Morbidity scoring and statistical analysis

Acute and late morbidity were graded according to the RTOG toxicity criteria. The incidence of late toxicity was scored at $\geq$3 months after the end of RT. The actuarial locoregional control (LRC), overall survival, and disease-free survival (DFS) rates were calculated using the Kaplan-Meier method. The log–rank test was used to assess the correlation of these endpoints with the clinical and therapeutic variables. Multivariate analysis was carried out with the Cox proportional hazard model. Fisher's exact test (two-tailed) and the chi-square test were used to evaluate differences in proportions. A difference with a p value of <0.05 was considered statistically significant.

Table 2. Incidence of Grade 3–4 acute toxicity (n = 281)

Organ/tissue	n (%)
Mucosa	
Grade 3	185 (66)
Grade 4	3 (1)
Larynx	
Grade 3	12 (4)
Grade 4	1 (0.5)
Skin	
Grade 3	46 (16)
Grade 4	0
Dysphagia	
Grade 3	114 (41)
Grade 4	4 (1.5)

Table 3. Grade 2 late complication distribution (n = 237)

Organ/tissue	n (%)*
Mucosa/submucosa	19 (8)
Larynx	28 (12)
Skin/subcutanuous	30 (12.5)
Dysphagia	5 (2)
Xerostomia	85 (36)
Trismus	4 (2)
Neurologic	2 (1)
Ear	11 (4)

* One patient may present with more than one complication.

RESULTS

Compliance

Twenty patients (7%) had a treatment interruption (seven for acute toxicities and two for lack of compliance) with a median interval of 5 days (range, 2–35 days). The median overall treatment time was 40 days (range, 28–79 days). The median tumor dose for all the patients was 69.9 Gy (range, 62.5–72.9 days). Only 1 patient did not receive the total prescribed dose. For concomitant chemotherapy, 80% of patients received the two cycles and 20% received one cycle, with the second cycle eliminated mainly because of toxicity.

Acute toxicity

Precise grading of acute toxicity was unavailable in 15 patients (5%). Table 2 reports the incidence of Grade 3 + 4 acute toxicity for the main organs. At least one Grade 3-4 acute toxicity was observed in 218 patients (77%), primarily mucositis; 3% had Grade 4 toxicity, mostly dysphagia. Fifty-four patients (18%) had to be hospitalized during or after treatment for a median duration of 19 days (range, 2–150 days). For nutritional support, a nasogastric tube or gastrostomy was required in 110 patients (37%), before (5%), during (28%), or after (5%) RT, with a median duration of 40 days (range, 2–1200 days). The median weight loss was 4.1 kg (range, 1–19.5 kg). Generally, increased toxicity was associated with advanced T and N stage, and patients with an advanced T or N stage were more likely to require gastrostomy or a nasogastric tube during RT (p = 0.0024 and p = 0.015, respectively). No statistically significant difference was seen between old and young patients (separated by the median) for nutritional support or hospitalization, nor in acute toxicity rate (p = 0.32). However, patients treated with concomitant chemotherapy had significantly increased rates of acute toxicity (87% vs. 73%, p = 0.009), nutritional support (p <0.0001), and hospitalization (p = 0.01).

Late toxicity

Of the 296 patients, 237 (80%) were assessable for long-term complications (patients with a minimal follow-up of 3 months and with available data). Of the 237 patients, 113 (48%) presented with Grade 2 late complications (Table 3) and 33 (14%) with Grade 3-4 late complications. The Grade 4 complications consisted of 7 cases of laryngeal edema/cartilage necrosis, 5 cases of mucosal necrosis, and 5 cases of mandibular bone necrosis. No statistically significant association between advanced T stage (p = 0.45) or the addition of chemotherapy (p = 0.43) and Grade 3-4 late toxicities was noted, and a trend toward greater late toxicity was suggested for advanced N stage (p = 0.058) and advanced age (p = 0.06).

Treatment-related deaths

Six patients (2%) died during the 6 months after RT: 2 of malnutrition, 1 of candida septicemia, 1 of pneumonia, 1 of massive hemorrhage, and 1 of an unknown cause after adjuvant chemotherapy. In addition, 2 patients died at 12 and 18 months of severe dysphagia and oropharyngeal hemorrhage, respectively. Although in some cases a direct link to treatment was not evident because of the unknown disease status, we considered all those deaths as potentially treatment related. Three patients had been treated with RT alone (1.5%) and five with concomitant RT and chemotherapy (6%; p = 0.12).

Clinical outcome

At last follow-up, 130 patients were still alive, and 4 were lost to follow-up (at 4–18 months). The 5-year actuarial overall survival rate was 44%. Of the 162 patients who had died, head-and-neck cancer was considered the cause of death in 87, treatment complications in 8, a second cancer in 34, intercurrent disease in 29, and unknown causes in 4. The median follow-up for the surviving patients was 55 months (range, 10–138 months). Seventy patients presented with local or regional failure and 37 patients presented with distant metastases, either alone or associated with locoregional failure.

Locoregional control

Without taking into account salvage surgery, the 5-year actuarial LRC rate for all patients was 72% (Fig. 1). Table 4 displays the main factors studied in the univariate analysis. In addition to the T, N, and UICC stage, patient perfor-

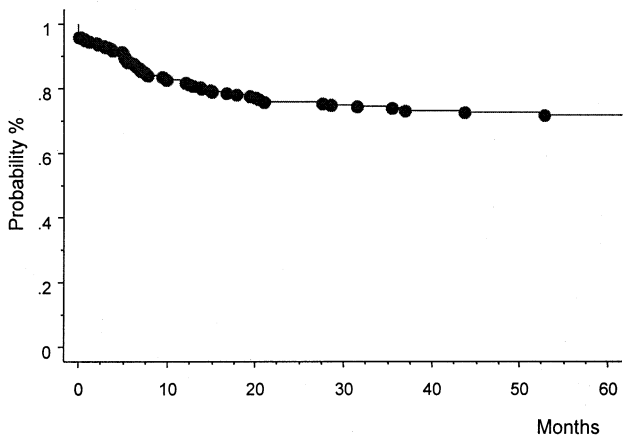

Fig. 1. Actuarial locoregional control for all patients.

mance status was a statistically significant factor, and patients with poorly differentiated carcinomas had a trend toward a statistically significant greater 5-year LRC rate compared with those with well to moderately differentiated carcinomas ($p = 0.09$). In the multivariate analysis, owing to the statistically significant association between patient performance status and treatment strategy ($p = 0.01$) and a trend to a statistically significant association with tumor differentiation ($p = 0.1$), the analysis was done by stratifying by treatment category (RT vs. RT plus chemotherapy) and by forcing tumor differentiation into the model. Thus, in a model in which all variables associated with a p value of <0.05 were included (except linked variables), only T and N stage remained significant; a trend toward a statistically significant impact was observed for tumor differentiation.

Disease-free survival

The actuarial DFS rate for all patients was 61% at 5 years. The results of the univariate analysis are displayed in Table 4. Tumor classification (T, N, UICC stage) and performance status were found to be statistically significant factors. In the multivariate analysis using a model constructed as mentioned above, only T and N stage retained their independent prognostic value, and performance status showed a trend toward a statistically significant impact.

Subgroup analysis

According to anatomic tumor subsite, the 5-year LRC rate was 38% for oral cavity, 62% for hypopharynx, 74% for oropharynx, 78% for nasopharynx, and 85% for larynx tumors. However, differences in stage distribution and treatment strategy (RT vs. RT plus chemotherapy) between the different subsites prevented any relevant direct comparison.

Table 4. Univariate analysis of clinical and therapeutic factors

Factor	Patients (n)	5-year LRC (%)	p	5-year DFS (%)	p
Clinical factors					
Age (y)					
<59	142	72	0.89	61	0.62
≥59	142	71		60	
Gender					
Male	221	71	0.43	58	0.17
Female	63	75		68	
WHO performance status					
0	174	77	0.007	67	0.001
1–3*	110	64		48	
Tumor differentiation					
Well-moderate	177	70	0.09	60	0.62
Poor	67	81		64	
TN stage (UICC 1997)					
T1–2/T3–4	137	80	0.0001	70	0.0001
	147	62		52	
N0/N1–3	116	79	0.018	73	0.0008
	168	67		52	
UICC stage					
I-II	68	80	0.023	79	0.0003
III-IV	216	69		55	
Therapeutic factors					
Chemotherapy					
No	192	71	0.64	60	0.63
Yes	92	73		62	
Overall treatment time (d)					
<40	126	73	0.64	63	0.8
≥40	158	71		59	

Abbreviations: WHO: World Health Organization; LRC = locoregional control; DFS = disease-free survival; UICC = Union Internationale Contre le Cancer.

* Unknown status included.

For example, Stage T3-T4 and N1-N3 accounted for 61% and 39%, respectively, for the oral cavity; for larynx tumors, the corresponding rates were 55% and 18%. The 5-year DFS rate was 30% for oral cavity, 50% for hypopharynx, 62% for nasopharynx, 63% for oropharynx, and 75% for larynx tumors. In patients presenting with Stage III-IV disease, the 5-year LRC rate was 66% for patients treated with RT alone and 72% for patients treated with combined RT and chemotherapy ($p = 0.18$). The corresponding rates for DFS were 51% and 62% ($p = 0.07$).

DISCUSSION

A range of different regimens has been developed for accelerating RT delivery in head-and-neck cancers, including very accelerated continuous schedules (7), split-course accelerated schedules (8), and concomitant boost schedules (5, 6). Although some of these regimens have demonstrated superiority in terms of locoregional control, the gain in overall survival has been modest at best (1, 9). Nevertheless, some useful lessons can be drawn from these studies. These include the poor tolerance of some highly accelerated schedules (10); the importance of the absolute time to deliver a dose of 70 Gy; and the importance of the total dose when a very accelerated schedule is envisioned. Indeed, in the EORTC trial 22851 (1), a significant gain in LRC was obtained in the accelerated arm, but at the expense of an unacceptable rate (52%) of Grade 3-4 late complications. Considering the lack of survival benefit, the findings of this study suggest the nonfeasibility of delivering 72 Gy in an absolute time of 25 days, even if a gap of 12–14 days is introduced to compensate for acute toxicity. In the Continuous Hyperfractionated Radiation Therapy (CHART) trial (7), a reduction in the total dose allowed the administration of a very accelerated schedule without increasing late complications, but without clinical gain. Thus, moderately accelerated regimens may represent the best compromise, because they allow the administration of doses of about 70 Gy in 5–6 weeks, without dramatically increasing the late complication rate (4, 6, 9).

Despite their superiority in terms of LRC, the implementation of accelerated RT schedules as routine practice in unselected patients is not well established. Several reasons may contribute to this, including the inherent inconvenience (multiple daily fractions, with potential logistical problems for both patients and staff), and the greater rate of acute toxicities requiring more intensive management, particularly when adding concomitant chemotherapy. With these aspects in mind, we considered it worthwhile to analyze our 10-year experience with the routine use of a concomitant boost RT schedule as standard radical head-and-neck cancer treatment.

As expected, acute toxicity was dominated by a high rate (77%) of Grade 3-4 mucosal reactions, with 42% of patients experiencing at least Grade 3 dysphagia and 37% needing nutritional support. Acute toxicity was significantly increased in patients with advanced T and N stages, reflecting the use of wider RT fields, as well as in those receiving concomitant chemotherapy, compatible with findings from prior studies (11, 12). However, acute toxicity appeared to be similar in younger and older patients, suggesting that this schedule is suitable for elderly patients who are physically fit enough to receive curative treatment. The considerable acute toxicity appeared to have little impact on compliance, in that the rate of treatment interruption (7%) was similar, or even inferior, to that observed with standard fractionation or with other 5-week accelerated regimens (1, 7, 13).

Serious long-term morbidity, although far from negligible, remained within the range expected with radical treatment of locally advanced head-and-neck cancers. The 14% rate of Grade 3-4 complications can be considered acceptable compared with the higher rates observed with certain other accelerated regimens used alone (1, 10) or combined with chemotherapy (12). In addition, deaths presumed to be treatment related were encountered in 1.5% of patients treated with RT alone and in 6% of patients who received combined treatment. This underscores the need for careful selection of patients for combined therapy, including standard evaluation criteria of general health status and the associated comorbidities, and for careful attention to patient compliance in the follow-up program for management of treatment toxicity. We recommend that patients anticipated to show poor compliance be excluded from combined therapy and that nutritional support be implemented before acute toxicity becomes severe.

In terms of treatment outcome, our 72% actuarial 5-year LRC rate can be considered comparable to the best results (54–66%) published from randomized trials concerning only selected patients (1, 4, 9). Moreover, the 61% actuarial DFS rate appears similar, or even superior, to the results reported from prospective studies using combined accelerated RT and chemotherapy (14, 15). Randomized trials have demonstrated the superiority of concomitant combined treatment over RT alone in terms of both LRC and, to a lesser extent, overall survival (16). Most combined modality trials used standard RT fractionation, split-course RT, and/or mono-drug chemotherapy to limit acute toxicities. The concomitant use of full-dose altered RT fractionation and chemotherapy is likely to represent the next step in increasing the aggressiveness of treatment. Data based on such approaches are scarce. In a randomized multicenter study (14) comparing a concomitant-boost RT regimen with or without concomitant chemotherapy (carboplatin and 5-fluorouracil), LRC was somewhat greater at 2 years in the combined treatment group (51% and 45%). However, late swallowing problems, including feeding tube dependency, were significantly greater among the combined modality patients (51% vs. 25%, $p = 0.02$). In the present series, patients presenting with Stage III-IV disease who received chemotherapy had somewhat superior 5-year LRC and, particularly, DFS ($p = 0.07$) compared with those of patients treated with RT alone. As mentioned above, these results were obtained at the price of significantly greater

acute toxicity and a greater rate of Grade 3-4 late complications (20% vs. 12%).

In the absence of proven superiority of a particular altered fractionated RT schedule for treating unfavorable head-and-neck cancers, the preference for one regimen over another will be determined by the toxicity profile, convenience, and the feasibility of its administration simultaneously with chemotherapy. The toxicity profile of the present concomitant boost schedule has now been well defined. Moreover, the feasibility of delivering chemotherapy concomitantly with this accelerated regimen has been demonstrated, because acute toxicities were manageable in selected patients, provided that timely supportive care could be provided. Finally, considering the convenience of the present program for both patients and technical staff, it should be considered as a valid accelerated regimen for adoption as routine radical treatment of head-and-neck cancers.

REFERENCES

1. Horiot JC, Bontemps P, van den Bogaert W, *et al.* Accelerated fractionation compared to conventional fractionation improves loco-regional control in the radiotherapy of advanced head and neck cancers: Results of the EORTC 22851 randomized trial. *Radiother Oncol* 1997;44:111–121.
2. Knee R, Fields RS, Peters LJ. Concomitant boost radiotherapy for advanced squamous cell carcinoma of the head and neck. *Radiother Oncol* 1985;4:1–7.
3. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: Altered fractionation regimens. *Lancet Oncol* 2002;3: 693–701.
4. Fu KK, Pajak TF, Trotti A, *et al.* A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16.
5. Ang KK, Peters LJ, Weber RS, *et al.* Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. *Int J Radiat Oncol Biol Phys* 1990;19:1339–1345.
6. Allal AS, Bieri S, Miralbell R, *et al.* Feasibility and outcome of a progressively accelerated concomitant boost radiotherapy schedule for head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1997;38:685–689.
7. Dische S, Saunders M, Barrett A, *et al.* A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1997;44:123–136.
8. Wang CC, Blitzer PH, Suit H. Twice-a-day radiation therapy for cancer of the head and neck. *Cancer* 1985;55:2100–2104.
9. Overgaard J, Hansen HS, Grau C, *et al.* The DAHANCA 6&7: A randomized multicenter study of 5 versus 6 fractions per week of conventional radiotherapy of squamous cell carcinoma of the head and neck. *Radiother Oncol* 2000;56(Suppl. 1):S4.
10. Peracchia G, Salti C. Radiotherapy with thrice-a-day fractionation in a short overall time: Clinical experience. *Int J Radiat Oncol Biol Phys* 1981;7:99–104.
11. Allal AS, Bieri S, Miralbell R, *et al.* 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. *Ann Oncol* 1997;8:681–684.
12. Bourhis J, Lapeyre M, Tortochaux J, *et al.* Preliminary results of the GORTEC 96-01 randomized trial, comparing very accelerated radiotherapy with radio-chemotherapy for locally inoperable HNSCC. *Int J Radiat Oncol Biol Phys* 2001; 51(Suppl. 1):39.
13. Allal AS, de Pree C, Dulguerov P, *et al.* Avoidance of treatment interruption: An unrecognized benefit of accelerated radiotherapy in oropharyngeal carcinomas? *Int J Radiat Oncol Biol Phys* 1999;45:41–45.
14. Staar S, Rudat V, Stuetzer H, *et al.* Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—Results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:1161–1171.
15. Wendt TG, Grabenbauer GG, Rodel CM, *et al.* Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. *J Clin Oncol* 1998;16:1318–1324.
16. Pignon JP, Bourhis J, Domenge C, *et al.,* for the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. *Lancet* 2000;355:949–559.