

## AVOIDANCE OF TREATMENT INTERRUPTION: AN UNRECOGNIZED BENEFIT OF ACCELERATED RADIOTHERAPY IN OROPHARYNGEAL CARCINOMAS?

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**Purpose:** To assess the impact of treatment interruption on the potential gain in locoregional control obtained with accelerated radiotherapy (RT) compared with conventionally fractionated RT in patients with oropharyngeal carcinomas.

**Methods and Materials:** 152 patients treated with radical RT for oropharyngeal carcinomas between 1979 and 1996 were retrospectively analyzed. According to the American Joint Committee on Cancer (AJCC) staging system, there were 6/30/43/73 stages I/II/III/IV. Sixty-one patients were treated with a conventional RT schedule (median dose 70 Gy in 35 fractions), and 91 patients with either of two 5/5.5-week accelerated RT schedules (median dose 69.6–69.9 Gy in 41 fractions). Discounting weekends, RT was interrupted for 2 consecutive days or more in 53 patients (median duration 11 days, range 2–97), including 67% of the patients in the conventional RT group and 13% in the accelerated RT group. Median follow-up for surviving patients was 55 months (range 23–230). The Cox proportional hazards model was used for the multivariate analysis of factors influencing locoregional control.

**Results:** In univariate analysis, factors associated with a significant decrease in locoregional control included WHO performance status  $\geq 1$ , advanced AJCC stages (III and IV), conventional RT fractionation, overall treatment time  $\geq 44$  days (median), and RT interruption. In the multivariate analysis, when introduced into the model individually, the three significant therapeutic factors remained significant after adjustment for the forced clinical variables. However, when the three therapeutic factors were introduced together into the model, beside the AJCC stage ( $P = 0.017$ ), only RT interruption remained a significant independent adverse prognostic factor ( $P = 0.026$ ).

**Conclusions:** This multivariate analysis highlights the potential negative impact of treatment gaps on locoregional control in oropharyngeal carcinomas. This suggests that treatment interruption may be an even more important parameter than the type of RT schedule per se. Thus, when assessing the relative merit of two RT schedules, inclusion of the other therapeutic factors in a multivariate model is mandatory in order to avoid misinterpretation of the results. © 1999 Elsevier Science Inc.

Accelerated radiotherapy, Treatment interruption, Oropharynx carcinomas.

### INTRODUCTION

In the treatment of head and neck cancer, unconventionally fractionated radiotherapy (RT) schedules have been associated in some studies with an increase in locoregional control compared with that obtained using monofractionated RT (1, 2). Based on evidence suggesting that increasing overall treatment time (OTT) is detrimental to locoregional control, accelerated RT programs have been intensively investigated during the past two decades. However, most clinical data regarding the importance of OTT came from series using conventionally fractionated RT, where treatment interruptions constituted the main cause of prolonged OTT (3, 4). Besides considerably shortening OTT, accelerated sched-

ules may also be associated with the potential advantage of minimizing treatment interruptions (1, 5). To assess the impact of treatment interruption as a confounding factor potentially influencing locoregional control, we undertook a multivariate analysis of a retrospective cohort of patients treated with different RT schedules for oropharyngeal carcinomas.

### MATERIALS AND METHODS

During the 17-year period of the present study (1979–1996), patients with oropharynx carcinomas referred for radical RT at Geneva University Hospital were, with few

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Table 1. Patients' characteristics (152 patients)

Age, years	59 (37–81)
Gender (male/female)	123/29
Performance status (WHO)	
0/1	65/59
2/3	20/3
Unknown	5
Tumor location	
Tonsillar fossa	76
Faucial arch	26
Base of tongue + vallecula	24
Posterior wall	6
Overlapping subsites	20
T stage (UICC 1992)	
T1/T2	20/48
T3/T4	61/23
N stage	
N0/N1	62/26
N2/N3	52/12
AJCC stage	
I/II/III/IV	6/30/43/73

WHO = World Health Organization; UICC = Union Internationale Contre le Cancer; AJCC = American Joint Committee on Cancer.

exceptions, treated with one of three main RT schedules. In the initial period a conventional RT schedule was used, delivering one daily fraction, 5 days/week to a total dose of 70 Gy. Starting in 1985, an accelerated schedule was used to deliver 69.6 Gy in 41 fractions over 5 weeks (ART-1). Since 1991, an accelerated concomitant boost RT schedule has been adopted, delivering 69.9 Gy in 41 fractions over 5.5 weeks (ART-2). The two latter schedules have been described in detail in previous publications (6, 7), and their adoption represented successive changes in treatment policy. To preserve some homogeneity in the RT approach, we excluded 18 patients treated with schedules other than the three described above, as well as four patients receiving a RT dose less than 60 Gy, and four patients with unknown locoregional control at last follow-up. Thus, of the 178 patients treated during the study period, 152 were included in the present analysis. Patients' characteristics are presented in Table 1. All tumors were squamous cell carcinomas.

#### Radiation therapy

The RT technique remained essentially the same over time, most of the patients having been treated with two opposed lateral fields and one anterior supraclavicular field. The boost technique was individualized according to the involved sites. All patients were treated with megavoltage photon beams ( $\text{Co}^{60}$  or 6–10 MV x-rays). The median tumor dose in the conventional RT schedule was 70 Gy (range 60–78 Gy) given in 2-Gy fractions (range 1.7–2), 5 times/week. The median tumor dose in ART-1 was 69.6 Gy (range 64.8–73.6 Gy) and that in ART-2 was 69.9 Gy (range 62.5–70.7). The dose delivered to the negative cervico-supraclavicular areas was 45–50 Gy. The median over-

all treatment time was 43 days (range: 35–144) for all patients, 57 days (range: 44–144) for patients treated with conventional RT, and 40 days (range: 35–79) for patients treated with the two ART schedules. Discounting weekends, RT was interrupted for 2 consecutive days or more in 53 patients (median duration 11 days, range 2–97). The rate of RT interruption was 67% and 13% for patients treated with conventional RT and accelerated RT, respectively. The stated reasons for RT interruption were acute toxicity and/or lack of compliance (38 patients), technical problems or holidays (11 patients), intercurrent disease (2 patients), and unknown (2 patients).

#### Surgery

Although patients having had radical surgery to the primary tumor were excluded from the present analysis, patients with N3 or bulky N2 neck disease were managed when possible surgically. Thus, 20 patients underwent a planned radical or modified neck dissection prior to RT. There were 7 such patients (11.5%) in the conventional RT group and 13 (14%) in the accelerated RT group. Otherwise surgery was reserved for the potential treatment of locoregional failures.

#### Chemotherapy

In the absence of medical contraindications, chemotherapy was usually offered to patients with T3–4 or N3 tumors. Fifty-two patients received neoadjuvant and/or concomitant chemotherapy. All the regimens consisted of 5-fluorouracil and cisplatin, while 19 patients in the initial period of the study also received epirubicin. The median number of cycles was 3 (range 1–8). In the conventional RT group, 19 patients (31%) received chemotherapy (one concomitantly with RT), and in the accelerated RT 33 (36%) patients received such a treatment (19 concomitantly with RT).

#### Statistical methods

Locoregional failure refers to primary tumor persistence or recurrence in the oropharynx area and/or to persistence or recurrence of metastatic lymph nodes in the cervico-supraclavicular area after the initial treatment. Actuarial locoregional control was calculated by the product-limit method (8). The logrank test was used to evaluate the correlation of locoregional control with selected clinical variables (age, sex, World Health Organization [WHO] performance status, AJCC stage, and tumor location) and treatment parameters (type of RT schema, OTT, treatment interruption, and use of chemotherapy). Multivariate analysis used a Cox proportional hazards model (9). As the present study focused on treatment-related factors, clinical variables shown to be significant in the univariate analysis or judged to be of obvious importance were forced into the Cox model. In this model the different parameters were analyzed, when possible, as continuous variables.

Table 2. Univariate analysis of clinical and therapeutic factors (152 patients)

	No. of patients	% 5-year locoregional control	<i>P</i>
<b>Clinical factors</b>			
Age			
<59/≥59 years	77/75	57/56	0.79
Gender			
Male/female	124/28	58/54	0.67
WHO performance status			
0/1/2–3*	65/59/28	66/50/49	0.03 <sup>†</sup>
Tumor subsite location			
Tonsillar fossa/others	75/77	56/58	0.73
Tumor differentiation			
Well/moderately/poor/unknown	55/47/33/17	59/49/60/62	0.69 <sup>†</sup>
AJCC stage			
Stage I–II/III/IV	37/43/72	70/57/48	0.011 <sup>†</sup>
<b>Therapeutic factors</b>			
RT fractionation			
Conventional/accelerated	61/91	47/61	0.02
Chemotherapy			
No/yes	100/52	60/50	0.10
Overall treatment time			
<44 days/≥44 days	77/75	63/48	0.008
RT interruption			
No/yes	99/53	66/37	<0.0001

\* Unknown status included in category 2–3.

<sup>†</sup> Test for linear trend.

## RESULTS

### Overall

The median follow-up for the 49 surviving patients was 55 months (range 23–230). At last follow-up, 58 patients had presented with locoregional failures (49 local ± regional/distant metastasis and 9 regional ± distant metastasis). The 5-year actuarial locoregional control for all patients was 57% (95% CI, 48–66%).

### Factors correlated with locoregional control

In univariate analysis, factors associated with a significant decrease in locoregional control included less favorable WHO Performance Status (≥1), advanced AJCC stages (III and IV), conventional RT fractionation, OTT ≥44 days (median), and RT interruption (Table 2).

In the multivariate analysis the significant clinical factors (Performance Status, AJCC stage), as well as patient age (continuous variable), were forced into the model. When introduced into the model individually, the three significant therapeutic factors remained significant when adjusted for the forced clinical variables. However, when the three therapeutic factors were introduced together into the model and adjusted for the above selected clinical factors, beside the AJCC stage ( $P = 0.017$ ), only RT interruption remained a significant independent adverse prognostic factor for locoregional control ( $P = 0.026$ ) (Table 3).

To assess the “true” impact of RT fractionation schedule on locoregional control, we restricted the analysis only to patients who completed RT without interruption. The actu-

arial 5-year locoregional control was 51.5% and 67.6% in the conventional and accelerated RT groups respectively ( $P = 0.14$ ).

## DISCUSSION

Strengthened by clinical observations suggesting an adverse effect of prolongation in OTT on local control, the notion that tumor cell repopulation during RT should influence the choice of fractionation schedules has gained increasing acceptance. In particular, this hypothesis predicted that shortening OTT by accelerating RT delivery would improve locoregional control in head and neck cancers (10, 11). Recently, two large European randomized trials appear to confirm this concept, with a significant gain in locoregional control reported in the accelerated RT arm in the European Organization for Research and Treatment of Cancer (EORTC) 22851 trial (1) and a trend to better results for

Table 3. Multivariate analysis of clinical and therapeutic factors for locoregional control (152 patients)

Prognostic factors	HR estimate	95% CI	<i>P</i> -value
AJCC stage			
I–II/III/IV	1.59	1.09–2.34	0.017
RT interruption			
No/yes	2.16	1.1–4.25	0.026

HR = hazard ratio.

some subgroups in the continuous hyperfractionated accelerated radiation therapy (CHART) trial (5). However, despite these rather positive results, it remains unclear to what extent the apparent superiority of accelerated RT is due mainly to shortening OTT. In particular, accelerated RT may owe some of its efficacy to the greater likelihood of such more rapid schedules to be completed without significant interruptions.

To our knowledge, the present study is the first to specifically address this particular question. In the published analyses of the two randomized European trials mentioned above, it is noteworthy that compliance was better in the accelerated arms in terms of treatment interruption (less frequent by a factor of 2 to 3) and to a lesser extent tumor dosage. However, in neither of these studies was treatment interruption taken into consideration in the multivariate analysis, despite its known potential adverse effect. This observation raises the question as to whether the overall gain obtained with RT acceleration was due solely to the acceleration effect, or to additional favorable therapeutic factors such as avoidance of treatment gaps.

The observation that actual overall treatment time is often longer than the projected one was made by Harari and Fowler (12) in an editorial discussing factors influencing treatment gaps and their possible consequences. Consistent with observations from randomized trials, we found that unplanned treatment gaps were much more frequently observed in patients receiving conventionally fractionated RT schedules. However, the 67% rate of RT interruption in the present series seems very high, viewed within the context of current treatment practices. Multiple factors may have contributed to this, including less awareness of the potential adverse effect of RT prolongation, as well as possible differences in the various physicians' appreciations of the acute toxicities and in their management. On the other hand acute morbidity, generally higher for accelerated regimens, would intuitively be expected to induce more RT interruptions in these patients. That this does not necessarily happen may reflect the shorter time between the onset of severe toxicity and the end of treatment, as is generally seen in accelerated schedules. Patients may more easily accept a short time with severe toxicities than a longer period with somewhat less toxicity. As mentioned above, data from recent prospective studies tend to confirm this notion by showing less patient compliance in conventional RT

arms. A protracted treatment schedule might thus be an indirect cause of unplanned RT interruptions, which may in themselves contribute to the clinical impression that conventional regimens are less effective than accelerated ones.

To try to shed light on this question we carried out an analysis assessing the impact of treatment gaps of 2 days or more in a cohort of patients with oropharyngeal cancers treated with either conventional RT or with 5–5.5 week accelerated regimens. In the monivariate analysis, the type of RT schedule significantly affected locoregional control (in favor of the accelerated regimen) and remained a significant factor in the multivariate analysis when entered alone into the model with the pertinent clinical factors. When treatment interruption was added to the multivariate model, RT schedule was no longer retained as a significant prognostic factor. This implies that RT interruption may have contributed in a major way to the inferior locoregional control obtained using conventional RT compared with the accelerated RT group.

This latter hypothesis merits further study, ideally within the framework of prospective trials. Indeed, the present retrospective analysis can at best serve to incite discussion and stimulate subsequent research. There were obviously many potential sources of selection bias inherent to our study design, including patient selection for neck surgery, chemotherapy indications, and different approaches to staging, corresponding to the gradual introduction of CT imaging during the 1980s. Such factors may all have had an influence on the oncologic results. However, except for CT staging, the other parameters were relatively equally balanced over time, whereas RT technique and equipment remained essentially unchanged. Even when considering the limitations of such a retrospective analysis, the result obtained here should be considered as provocative. In controlled trials treatment interruption can obviously not be considered as a stratification variable at the time of randomization, since it can be defined only after completion of treatment. Nonetheless, it seems of manifest importance to take this factor into consideration when comparing the results of two RT schedules that are assumed to differ principally due to differences in planned OTT. Failure to take all relevant therapeutic factors into consideration may lead to misinterpretation of the results of trials comparing different fractionation programs.

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