Concomitant Boost Radiotherapy in Oropharynx Carcinomas

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Fifty-five patients with resectable and unresectable oropharynx carcinomas were treated with concomitant boost radiotherapy. Forty-two of the patients (76%) had stages III–IV disease. Although none of the patients had undergone major surgery to the primary tumor, 11 had neck dissections prior to radiotherapy, and 19 (35%) received chemotherapy. The planned total tumor dose was 69.9 Gy, delivered over 5.5 weeks. During the last 3.5 weeks, a boost to the initial gross disease was delivered in 13 fractions of 1.5 Gy each, as a second daily fraction in a progressively accelerated schedule; the prescribed dose outside the boost volume thus was 50.4 Gy. Median follow-up for surviving patients was 31.5 months (range: 16–65 months). All patients but one completed the planned radiotherapy schedule. According to the RTOG scoring system, 48 patients (88%) presented with grades 3–4 acute toxicity. The rate of grades 3–4 late complications was 12%. At three years the actuarial locoregional control rate was 69.5% and overall survival was 60%. We conclude that this concomitant boost schedule is feasible and does not seem to be associated with an excess risk of late complications. Acute toxicity was higher in association with chemotherapy, but remained manageable. Although the oncological results appear encouraging, evaluation of the efficacy of concomitant boost schedules compared with conventionally fractionated irradiation with or without concomitant chemotherapy requires prospective randomized trials.

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Depending on the site and stage of disease, the prognosis of patients with locally advanced oropharynx carcinomas treated by standard radiation therapy (RT) is generally unfavorable (1, 2). Oropharyngeal cancers tend to be deeply infiltrative, with early involvement of the tongue musculature and a high incidence of lymph node metastases at presentation (1). The two principal strategies aimed at improving curability consist of modified radiation fractionation schedules (2–5) and the addition of chemotherapy to RT (6, 7). Since the potential advantage of accelerated fractionation is at least partly mitigated by increased acute toxicity, the concept of volume reduction in conjunction with acceleration was introduced in the form of a 'concomitant boost' schedules (8). This schedule was based on the hypothesis that the onset of tumor clonogen repopulation may become significant about two weeks after the beginning of the RT and that its rate may increase progressively toward the end of the treatment (9).

Taking into account the encouraging preliminary results reported in the literature, a modified concomitant boost schedule was introduced in 1991 at the University Hospital of Geneva. For stages III–IV disease, chemotherapy was first added sequentially in selected cases, and then progressively more frequently in a concomitant fashion. This paper describes the feasibility, toxicity and therapeutic outcome of a pilot study in oropharynx carcinomas.

MATERIAL AND METHODS

Patients

From May 1991 to October 1995, 55 patients with oropharynx carcinoma were treated with radical RT, without major surgery to the primary tumor. Patients with metastatic disease or locoregional recurrence were excluded from the present study. Thirty-six patients were treated with RT alone, and 19 in combination with chemotherapy. Before radiation therapy, a uni- or bilateral neck dissection was performed in 11 patients. Otherwise, surgery was reserved for salvage of locoregional failures. Patients' staging included a complete medical history, physical examination, panendoscopy, chest x-ray, routine hematologic and serum chemistry profiles, and computerized tomography of the head and neck region. The clinical characteristics of the patients are presented in Tables 1 and 2.

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Table 1

Patient characteristics

Median age (range)	59 years (40–81, range)
Gender Male/Female	39/16
Tumor location	
Tonsil fossa	25
Base of tongue and vallecula	9
Pillars	4
Soft palate	4
Posterior wall	1
Oropharyngeal subsites	12
TN stage:	
T1-2	25
T3-4	30
N0	20
N1-3	35
AJCC stage:	
I–II	13
III	9
IV	33

Radiation therapy

The fractionation schedule can be summarized as follows: the extended field, including both the sites of macroscopic disease and the electively irradiated area, was treated with fractions of 1.8 Gy 5 days per week to a total dose of 50.4 Gy. The boost, encompassing gross disease only, consisted of 13 fractions of 1.5 Gy (19.5 Gy), given as a second daily fraction, starting on the last day of the second week, in a progressively accelerated fashion (Table 3). The minimum interval between the two daily fractions was 6 h. The total dose to gross disease was 69.9 Gy in 41 fractions over a period of 38 days.

The primary tumor and the upper neck nodes were generally irradiated through parallel opposed lateral fields, while the lower neck nodes, including both supraclavicular areas, were treated with one anterior field, using 6 MV beams in most patients. The field arrangement for the boost was individualized according to the tumor extent and location. Posterior triangle chains lymph nodes were boosted with electrons of appropriate energy in order to limit the spinal cord dose to less than 45 Gy. The areas treated electively received doses in the range of 45–50 Gy in 25–28 fractions. No specific technical modification of treatment volume or timing was used in the group of patients receiving chemotherapy.

Table 2

Clinical tumor and nodal stages

T and N stages	T1	T2	T3	T4	Total
N0	3	11	4	2	20
N1	1	3	–	3	7
N2	5	4	9	7	25
N3	–	–	3	–	3
Total	9	18	16	12	55

Chemotherapy

Chemotherapy was added for stages III–IV diseases, representing a group of more advanced stages. There was no difference in age and sex distribution. In the initial patients chemotherapy was delivered sequentially prior to starting RT. Satisfactory tolerance led to a shift toward the administration of an increasing proportion of the chemotherapy concomitantly with RT.

In 2 patients, chemotherapy was administered only prior to, and in 17 concomitantly with RT, either alone or with neoadjuvant and/or adjuvant chemotherapy. With the exception of 2 patients who received weekly carboplatin, all patients had cisplatin-based therapy (17 patients). Cisplatin was given with 5-fluorouracil (5-FU). Eleven patients received 3 cycles, and 6 patients received 2 cycles, administered generally on the first and fourth weeks of RT; the third cycle was administered after RT. The cisplatin (100 mg/m^2) was given as a rapid intravenous infusion followed by continuous 24-h intravenous infusions of 5-FU (1000 mg/m^2/d) for 5 days. During RT the 5-FU dose was reduced by 20–40% in the second course, depending on the severity of the acute mucosal reactions.

Statistical methods

The actuarial overall and disease-free survival rates as well as actuarial locoregional control rates were calculated by the Kaplan-Meier method (10). The Fisher exact test and the logrank tests were used to assess significant differences between simple proportions and survival curves, respectively.

RESULTS

All the patients but one completed the RT schedule as planned. Treatment was interrupted because of toxicity in two patients receiving concomitant chemotherapy, with split durations of 17 and 35 days. The median overall treatment time was 40 days (range: 36–79 days), compared with an average of 38 days in protocol. The median tumor dose for all the patients was 69.9 Gy (range: 62.5–71 Gy).

Morbidity

According to the RTOG grading system (11), grade 3 acute mucositis occurred in 43 patients (78%), and grade 4 in 2 patients. The median weight loss during RT was 4.7 kg (range: 0–14.6 kg). Twenty-two patients (40%) presented with grade 3 dysphagia. In patients receiving chemotherapy, grade 3 dysphagia was significantly more frequent than in those receiving RT alone (68% vs. 25%, $p = 0.003$). Twelve patients required hospitalization for nutritional support; the median length of hospitalization

Table 3

Schematic representation of the radiotherapy protocol

Week	1	2	3	4	5	6
Wide fields (50.4 Gy)	× × × × ×	× × × × ×	× × × × ×	× × × × ×	× × × × ×	× × ×
Boost (19.5 Gy)	-----	----×	×---×	×–×-×	×–× × ×	× × ×

was 14 days (range: 4–44 days). Patients receiving chemotherapy had a higher rate of hospitalization (37% vs. 14%, $p = 0.08$) and required a nasogastric tube (68% vs. 22%, $p = 0.001$) more frequently than patients treated with RT alone. Two patients died of treatment-related causes during the three months following RT. One patient treated with RT alone died from pneumonia as a consequence of severe laryngeal edema, and the other patient as a result of post-chemotherapy thrombopenia from a massive oropharyngeal hemorrhage.

Fifty-one patients with a minimum follow-up of 3 months were evaluated for complications. According to the RTOG grading system (11), 30 patients (59%) presented with grade 2 and 6 patients (12%) with grades 3–4 late complications. The grade 4 complications included one severe laryngeal edema, one oropharyngeal mucosal necrosis, and two mandibular bone necroses, all treated conservatively. Three of the grade 4 complications were in patients receiving chemotherapy.

Clinical outcome

The median follow-up for survivors was 31.5 months (range: 16–55 months). None of the patients was lost to follow-up. At the time of this analysis 23 patients had died. Head and neck cancer was considered the cause of death in 15 patients (65%), second malignancies in 3, intercurrent disease or acute complications in 4, and one patient died from unknown cause. 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. The 3-year actuarial locoregional control rate was 69.5% (see Fig. 1). The 3-year locoregional control rate was significantly higher for stages I–III than for stage IV (79% vs. 61%, $p = 0.005$). At 3 years the actuarial overall survival rate was 60%, with a disease-free survival rate of 65%.

DISCUSSION

The management of oropharyngeal carcinoma is controversial (1, 12). The choice of treatment depends on the extent of the primary tumor and the nodal status, the physical condition of the patient, as well as on other less well-defined parameters that may be institution-dependent. The options essentially consist of radical RT with or without neck dissection and primary surgery with or without post-operative RT, all of which may or may not be used with chemotherapy. Patient selection for one or another treatment approach may vary between institutions and over time, making any comparison of treatment results difficult, even when considering a single therapeutic modality. Except for the rare indication for purely transoral excision, the surgical techniques used for oropharyngeal cancers require the removal of part of the ascending ramus of the mandible and/or a portion of the lateral pharyngeal wall, tongue, and soft palate. As a result some patients are unable to return to a normal solid diet following radical surgery, and many centers prefer to restrict its use to clinical situations in which the probability of local control with RT is low.

Radiotherapy alone provides acceptable local control for most T1–3, N0-1 oropharyngeal carcinomas (1, 12–15). Reflecting the paramount importance of tumor volume, however, local control is a decreasing function of stage, and the prognosis of patients with locally advanced disease treated by monofractionated RT is generally unfavorable (2, 14, 16). In the hope of improving these results, clinical research has centered on the modification of RT fractionation schedules and the addition of chemotherapy to RT. In oropharynx cancers, a 10-day reduction in overall treatment time to around 5 weeks is estimated to yield a 10–15% improvement in local control (14). Among the various schedules of unconventional fractionation, the accelerated concomitant boost has gained use in many centers because of convenience (3, 17) and radiobiological

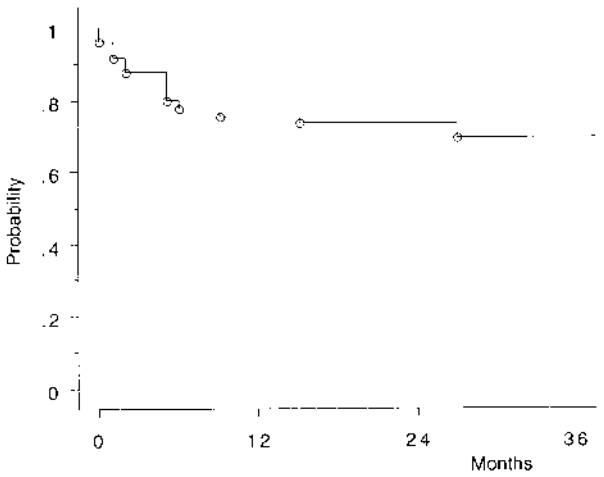

Fig. 1. Actuarial locoregional control for 49 patients having a minimum follow-up of one year.

Table 4

Results of different accelerated and hyperfractionated radiation therapy schedules for oropharynx carcinoma

Regimen	Patients n	Stages III–IV or T3–T4 in % and site	RT characteristics	Acute reactions	Late toxicities	Results
Accelerated with split						
Wang (5)						
1. B.i.d.–q.i.d.	52	75% T3–T4 Fauc. Tonsil and base of tongue	2 × 1.6 Gy/day 4-h gap, 10 days split, then 1.8 Gy/d TD 65 Gy	Not specified	Not specified	3-year LC 54%
2. B.i.d.–b.i.d.	88	50% T3–T4	2 × 1.6 Gy/day (b.i.d.–b.i.d) 6 h gap, 10-day split	Not specified	Not specified	3-year LC 85% The b.i.d.–b.i.d. is significantly better than the b.i.d.–q.d ($p = 0.0013$)
Concomitant boost						
Ang et al. (3)	79	48% T3–T4 Faucial pilar, soft palate, base of tongue	1.8 Gy/day + 1.5Gy/day, >4-h gap. TD 72 Gy	Mucositis 2: 12% Mucositis 3 and 4: 88%	Grade 4: 2.5%	2-year CSS 66% (without salvage surgery)
Hyperfractionation						
Pinto et al (4) Arm 1: conventional	48	83% T3–T4	2 Gy/day. Total dose 66 Gy (33 × 2) Gy	Mucositis 3: 65% Mucositis 4: 35%	Not specified	3.5-year OS 8%. 3.5-year CSS 7%
Arm 2: hyperfractionation	50	88% T3–T4. Base of tongue and oropharynx	2 × 1.1 Gy/day, 6-h gap. TD 70.4 Gy	Mucositis 3: 58% Mucositis 4: 48%	Not specified	3.5 year OS 27% 3.5 year CSS 25% The HF is significantly better than the CF ($p = 0.03$)
Horiot et al (2)						
Arm 1: conventional	159	54% III	2 Gy/day.TD 70 Gy. (35 × 2)	Mucositis 3: 49%	Grade 3: 16%	5-year LC 37%
Arm 2: hyperfractionation	166	58% III Exclusion base of tongue, oropharynx	2 × 1.15 Gy/day. 4–6 h gap. TD 80.5 Gy	Mucositis 3: 70%	Grade 3: 11%	5-year LC 57% The HF is significantly better than the CF ($p = 0.05$)

OS = overall survival; CSS = cancer-specific survival; DFS = disease-free survival; LC = local control; b.i.d = twice-daily; q.i.d = once-daily; TD = total dose; CF = conventional fractionation; HF = hyperfractionation.

rationale. By limiting the volume of tissue exposed to accelerated therapy, a reduction in overall treatment time on the order of 1.5–2 weeks is possible without requiring a reduction in the total dose or the introduction of a treatment break.

Although the present fractionation schedule was based on that developed at the University of Texas M. D. Anderson Cancer Center (3, 8), a modified concomitant boost delivery was introduced in Geneva, in which the 13-s 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 that the incremental dose required to compensate for tumor proliferation might increase progressively toward the end of the treatment (9, 18). Not unexpectedly, the therapeutic results appear similar to those found with other similar fractionation schedules (Table 4). The 69.5% 3-year locoregional control and 65% disease-free survival rates are comparable with those from other accelerated RT programs, and the high rate of grades 3–4 acute mucosal reactions is consistent with the values of 58–94% reported by other investigators (2, 3, 19).

Although there are thus far no data from randomized studies explicitly demonstrating the superiority of concomitant boost RT compared with standard RT, recent prospective data from accelerated fractionation support the notion that locoregional control can indeed be substantially improved (20). However, the particular study in question (20) had unacceptably increased late complications in the accelerated arm, suggesting that the particular schedule used in that study should not be recommended for general use. In the present series, despite the use of concomitant chemotherapy in 35% of cases, the rate of serious late complications (12%) remained acceptable in a previous paper, we described in some detail the feasibility of this RT regimen together with concomitant chemotherapy (21). Based on the results obtained, and the importance of the use of concomitant chemotherapy (6, 7), the present RT regimen may well represent one of the few accelerated programs for which such a combination might be feasible. The efficacy of concomitant boost RT compared with conventionally fractionated irradiation with or without concomitant chemotherapy merits further study in appropriate randomized prospective trials.

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