Randomized Trial of Radiation Therapy Versus Concomitant Chemotherapy and Radiation Therapy for Advanced-Stage Oropharynx Carcinoma

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Background: **We designed a randomized clinical trial to test whether the addition of three cycles of chemotherapy during standard radiation therapy would improve disease-free survival in patients with stages III and IV (i.e., advanced oropharynx carcinoma).** ***Methods:*** **A total of 226 patients have been entered in a phase III multicenter, randomized trial comparing radiotherapy alone (arm A) with radiotherapy with concomitant chemotherapy (arm B). Radiotherapy was identical in the two arms, delivering, with conventional fractionation, 70 Gy in 35 fractions. In arm B, patients received during the period of radiotherapy three cycles of a 4-day regimen containing carboplatin (70 mg/m^2 per day) and 5-fluorouracil (600 mg/m^2 per day) by continuous infusion. The two arms were equally balanced with regard to age, sex, stage, performance status, histology, and primary tumor site.** ***Results:*** **Radiotherapy compliance was similar in the two arms with respect to total dose, treatment duration, and treatment interruption. The rate of grades 3 and 4 mucositis was statistically significantly higher in arm B (71%; 95% confidence interval [CI] = 54%–85%) than in arm A (39%; 95% CI = 29%–56%). Skin toxicity was not different between the two arms. Hematologic toxicity was higher in arm B as measured by neutrophil count and hemoglobin level. Three-year overall actuarial survival and disease-free survival rates were, respectively, 51% (95% CI = 39%–68%) versus 31% (95% CI = 18%–49%) and 42% (95% CI = 30%–57%) versus 20% (95% CI = 10%–33%) for patients treated with combined modality versus radiation therapy alone (*P* = .02 and .04, respectively). The locoregional control rate was improved in arm B (66%; 95% CI = 51%–78%) versus arm A (42%; 95% CI = 31%–56%).** ***Conclusion:*** **The statistically significant improvement in overall survival that was obtained supports the use of concomitant chemotherapy as an adjunct to radiotherapy in the management of carcinoma of the oropharynx. [J Natl Cancer Inst 1999;91: 2081–6]**

Radiation therapy is the conventional treatment for locally advanced, nonresectable oropharynx carcinoma. However, therapeutic results are poor with this treatment modality, and chemotherapy has been used in an effort to improve therapeutic results. Induction chemotherapy may be useful in the selection of patients who are likely to benefit from nonsurgical organ-preservation treatment schemes *(1,2).* There is, however, no evidence that neoadjuvant chemotherapy followed by radiotherapy is more efficacious than radiotherapy alone *(3).* Concurrent administration of chemotherapy and radiotherapy is another promising approach for treating patients with locally advanced head and neck cancer. Phase I and II studies have indicated that concomitant radiotherapy and chemotherapy are feasible but are associated with acute toxicity enhancement, especially mucositis. By use of cisplatin or carboplatin alone, randomized studies of concomitant treatment have reported survival improvement *(4)* or no benefit *(5).* With the use of 5-fluorouracil (5-FU) alone, the study by Browman et al. *(6)* suggested a potential benefit of the concomitant regimen.

Other studies *(7,8)* have used a multidrug regimen with an alternating chemotherapy and radiotherapy regimen and reported better results compared with radiation therapy alone. Compared with sequential chemotherapy and radiotherapy, concomitant treatment appeared to be more efficacious *(9).*

Recently, three meta-analyses *(10–12)* have suggested that the impact of chemotherapy on survival in head and neck cancer is small but highly associated with the timing of chemotherapy. Concomitant administration of radiation therapy and chemotherapy led to an absolute benefit on 5-year survival of about 10%.

In 1994, within the French "Groupe d'Oncologie Radiothérapie Tête et Cou" (GORTEC), we initiated a prospective randomized, multicenter phase III clinical trial to test the hypothesis that conventional radiotherapy plus concomitant chemotherapy leads to a better disease-free survival than conventional radiotherapy

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alone. Carboplatin was used because of its reduced renal, digestive, and neurologic toxic effects compared with cisplatin and its high radiosensitizing effect, as suggested in at least one study *(13)*.

PATIENTS AND METHODS

Eligibility Criteria

The patients were evaluated by a multidisciplinary team consisting of an otolaryngologist and radiation and medical oncologists. All of the patients had medical histories taken and underwent physical examination, including endoscopic examination under anesthesia, esophagoscopy, chest x-ray film, and computed tomography of the head and neck. The tumors were classified according to the criteria of the International Union Against Cancer by use of the 4th edition of the TNM (tumor–node–metastasis) classification of malignant tumors *(14)*.

Patients were included in the study if all of the following were true: they had invasive squamous cell carcinoma of the oropharynx (stage III or IV, without evidence of distant metastases), they were less than 75 years old, and they had a Karnofsky performance score of at least 60. Patients were excluded if they had lost more than 20% of their body weight, if they had previously undergone treatment for this disease or any other cancer (except basal cell carcinoma of the skin), or if they had synchronous primary lesions. Other criteria for inclusion included a neutrophil count greater than 1500 cells/mm^3, a platelet count greater than 120 000 cells/mm^3, and a serum creatinine concentration of 1.4 mg/dL (120 μmol/L) or less. The protocol was approved by the regional ethics committee. Written informed consent was obtained from all patients. The study design is shown Fig. 1.

Treatment

Radiotherapy. The radiotherapy regimen was the same in both treatment arms according to the recommendations of the International Commission on Radiation Units and Measurements *(15)*. Radiation therapy was delivered by use of cobalt-60 gamma rays, 4- or 6-mV photons. The oropharynx tumor and the upper cervical lymph nodes were treated with two parallel, laterally opposed fields. The median, the lower part of the neck, and the supraclavicular lymph nodes were treated by use of a single anterior field with midline blocking. The inferior border of the lateral fields and the superior border of the anterior field coincided on the skin. All fields were treated at each session in both treatment arms. The total dose delivered to the primary tumor and the involved lymph nodes was 70 Gy (2 Gy per fraction, one fraction per day, and five fractions per week) without any planned interruption. Lateral field doses were prescribed at midplane. A supraclavicular field dose was prescribed at a 3-cm depth. If there were no palpable lymph nodes, 44 Gy was delivered in the lower part of the neck and in the spinal lymph nodes, and 56 Gy was delivered in the cervical areas adjacent to an involved lymph node area. Electron beams were used to give a boost to the posterior cervical lymph nodes. The dose to the spinal cord was kept below 44 Gy. Computed tomography scan dosimetry was performed to evaluate the maximal and minimal tumor doses.

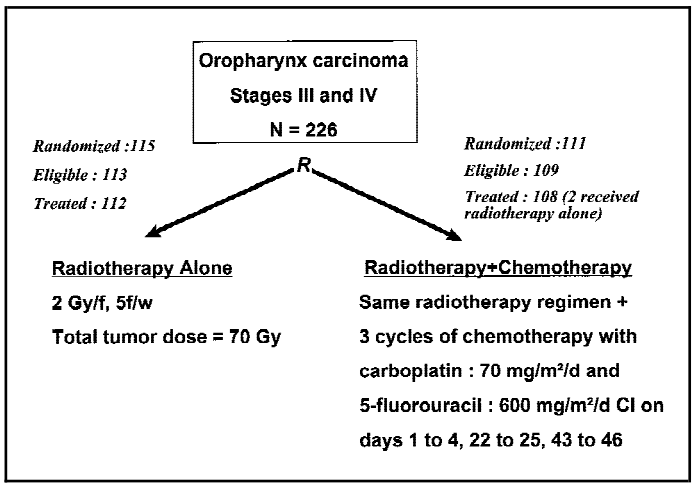

Fig. 1. Study design of the randomized trial.

Chemotherapy. In the experimental arm, patients received three cycles of chemotherapy given concurrently with radiation therapy during the 1st, 4th, and 7th weeks. Chemotherapy consisted of 5-FU and carboplatin. 5-FU was administered as a 24-hour continuous infusion at a dose of 600 mg/m^2 of body surface area per day for 4 days. Carboplatin was given as a daily bolus dose of 70 mg/m^2 per day for 4 days. Patients received antiemetics (metoclopramide and dexamethasone). The chemotherapy cycle was started on days 1, 22, and 43.

Follow-up: Quality Assurance

During treatment, the patients were examined at least weekly. Weight as well as mucosal and skin reactions were evaluated and scored according to the European Organization for Research and Treatment of Cancer scales for acute objective and functional mucosal reaction.

Follow-up evaluation was performed 6 weeks after the end of treatment and then every 4 months until death or the end of the study period. The first evaluation included a clinical examination and a computed tomography scan. Each 4-month evaluation included a clinical examination. Chest radiography and ultrasonography of the liver were performed each year. Locoregional or distant failures were considered as failures of treatment. Only the first failure in a patient was reported; subsequent sites of involvement were not recorded. After disease recurrence, the patients could be treated by any method considered to be useful. Late side effects were observed and scored in all patients and were analyzed in patients for whom locoregional control of the disease was obtained.

A quality-assurance program was established. It was realized by a team of independent reviewers, consisting of at least one radiation therapist and one radiation physicist. Quality control procedures included a review of the clinical chart (endoscopy and computed tomography scan) and all of the radiotherapy

Table 1. Patient characteristics according to treatment group*

Characteristic	RT (n = 113)	RT + CT (n = 109)
Male/female	101/12	99/10
Age, y		
Mean	54.4	55.7
Range	34–74	32–73
Stage III, No. (%)	35 (31)	36 (33)
Stage IV, No. (%)	78 (69)	73 (67)
Karnofsky index, No. (%)		
90–100	72 (64)	58 (53)
80	25 (22)	36 (33)
70	16 (14)	15 (14)
Histologic classification, No. (%)		
Well differentiated	52 (46)	53 (48)
Moderately differentiated	34 (31)	24 (22)
Poorly or undifferentiated	11 (10)	14 (13)
Unspecified	16 (13)	18 (17)
Primary tumor site, No. (%)		
Tonsillar region	42 (37)	43 (39)
Base of tongue	39 (34)	40 (37)
Soft palate-uvula	11 (10)	12 (11)
Posterior wall	7 (6)	8 (7)
Nonclassified	4	5
T classification, No. (%) (UICC)		
T1	3 (2)	5 (4)
T2	13 (12)	9 (9)
T3	58 (51)	52 (48)
T4	39 (35)	42 (39)
N classification, No. (%) (UICC)		
N0	27 (24)	29 (27)
N1	27 (24)	25 (23)
N2a	15 (13)	18 (17)
N2b	22 (19)	12 (11)
N2c	11 (10)	8 (7)
N3	11 (10)	16 (15)

*Because of rounding, percents do not always total 100. RT = radiotherapy; CT = chemotherapy; UICC = International Union Against Cancer.

chart entries (simulation and control films and dosimetry). This review was performed for all of the patients included in the study.

Randomization and Statistical Analysis

Patients were randomly assigned to a treatment group by a central office after their eligibility was established. Randomization was balanced by institution and clinical stage. The two treatment groups were compared with respect to baseline characteristics by use of the Student's *t* test for continuous variables and the chi-squared test for categoric variables. Gaussian distribution of the population was verified by use of the David–Hartley–Pearson test. When necessary, Fisher's exact test was used. To detect an improvement in 3-year overall survival from 25% in the radiotherapy-alone group to 40% in the combined-treatment group, with a one-sided type I error of .05 and a power of 80%, the intended number of randomly assigned patients was 220. Actuarial survival and disease-free survival were calculated according to the Kaplan–Meier method and compared with the stratified logrank test. All reported *P* values are two-sided and considered to be statistically significant for two-sided $P<.05$. Data on patients were analyzed according to the intention-to-treat principle. Survival was calculated from the date of random assignment to the most recent follow-up contact or to the date of disease recurrence or death and included all patients in the study. For survival, every death (regardless of cause) was considered as a failure. Since all of the patients were considered free of tumor at the end of therapy on the basis of clinical examination and CT scan, disease-free survival was used; every recurrence (whatever the type) and any death before recurrence was considered as a failure. All patients assigned to the treatment groups were included in all analyses of survival. No interim analysis was planned.

RESULTS

Patients

From July 1994 through September 1997, a total of 226 patients were enrolled. Four patients (two in each arm) were found to be ineligible. The reasons for ineligibility were the presence of another primary cancer in the esophagus (two patients) and distant metastasis (two patients). Thus, a total of 222 patients (113 assigned to radiotherapy alone and 109 assigned to combined treatment) remained in the analysis. Two patients were randomly assigned to the combined-treatment arm but treated with radiotherapy alone. Two patients died after random assignments before any treatment (one in each arm). All of these four patients were analyzed according to the intention-to-treat principle. The two treatment groups were similar, except for a slightly higher proportion of patients with N3 lymph nodes in the combined-treatment group (Table 1).

Compliance With Treatment

Among the 113 patients assigned to radiotherapy alone, one patient died before any treatment; three patients received less than 8 Gy (two because of early death and one because of refusal of treatment). Among the 109 patients assigned to the combined-treatment group, two were treated with radiotherapy alone (one because of refusal of chemotherapy by the patient and one because of an error); one patient died before any treatment was given. The mean total delivered dose of radiation was 69.2 and 69.6 Gy in the radiotherapy-alone arm and in the combined-treatment arm, respectively. Compliance with radiation therapy is shown in Table 2, A. No differences were observed regarding the frequency of treatment breaks. However, when a treatment break was decided because of toxicity, the mean duration of the radiotherapy interruption was longer in the combined-treatment arm than in the radiotherapy-alone arm: 6.2 days (95% confidence interval [CI] = 3.0–9.0 days) versus 8.9 days (95% CI = 4.0–12.0 days) ($P = .05$).

Table 2. Compliance with treatment

Table 2, A. Compliance with radiation therapy*

Radiation parameter	RT (n = 113)	RT + CT (n = 109)
Mean overall treatment time, days (range)	49.8 (1–77)	51.6 (1–82)
Treatment interruptions ⩾3 days (%)	16 (14)	19 (17)
Mean duration of treatment break, days (range)	6.2 (3–17)	8.9 (3–36)
Radiotherapy stopped before completion, No. (%)	6 (5%)	6 (5%)
Mean value of maximal tumor dose, Gy (range)	71.5 (4–82)	72.7 (6–82)
Mean value of minimal tumor dose, Gy (range)	66.8 (4–74)	67.7 (6–73)

Table 2, B. Compliance with chemotherapy†

	Cycle No.		
Chemotherapy	1	2	3
Chemotherapy dose			
5-FU, mg/m^2, mean dose (range)	2350 (0–2520)	2120 (0–2480)	1605 (0–2400)
5-FU, % of planned dose	98	88	67
Carboplatin, mg/m^2, mean dose (range)	275 (0–290)	241 (0–280)	185 (0–280)
Carboplatin, % of planned dose	98	86	66
Chemotherapy administration			
Full dose, no delay—No. of patients	104	80	51
Full dose with delay—No. of patients	0	8	5
Dose reduced—No. of patients	2	11	13
Dose reduced with delay—No. of patients	0	4	2
Not given‡	3	6	38

*RT = radiotherapy; CT = chemotherapy; 5-FU = 5-fluorouracil.

†Compliance was evaluated for all of the patients treated in the radiochemotherapy arm, including patients for whom chemotherapy was not administered. Doses of chemotherapeutic agents are given in milligrams per square meter of patient surface area.

‡Not given for 32 patients over 38 y of age because radiotherapy total dose was delivered.

Seventy-one of the patients (65%) in the combined-treatment group received the three cycles of chemotherapy concurrently with radiation therapy. Ninety-seven percent (106 patients) and 94% (103 patients) of the patients, respectively, received one and two cycles. Thirty-eight patients (35%) did not receive the third cycle because of a delay in chemotherapy administration. The third cycle was not offered to these patients for whom radiation therapy was over. The relative dose intensity (RDI) was 78% and 76% for carboplatin and 5-FU, respectively. The RDI is the ratio between the protocol dose intensity and the mean dose intensity actually administered to the patients, in which the dose intensity is expressed as the average dose per week (mg/m^2 per week) over the course of treatment. Compliance with chemotherapy is shown in Table 2, B.

Acute Toxicity

One patient died of treatment toxicity (febrile neutropenia and sepsis). Table 3, A, shows the acute toxicity of treatment. Hematologic toxicity was more frequent in the combined-treatment group, as expected with the use of chemotherapy agents. The incidence of grades 3 and 4 mucositis was higher in the combined-treatment arm than in the radiotherapy-only arm (71% versus 39%; 95% CI = 54%–85% and 29%–56%, respectively). In consequence, the nutritional status of the patients in the combined-treatment group was poorer, with a higher proportion of patients who lost more than 10% of body mass and who required temporary nasogastric or gastrostomy feeding tubes.

Survival

After a median follow-up of 35 months (range, 12–56 months), 116 patients had died (69 in the radiotherapy-only group and 47 in the combined-treatment group). The median survival was 15.4 months in the radiotherapy-only group and 29.2 months in the combined-treatment group. Patients in the combined-treatment group had a better rate of 3-year overall survival: 51% (95% CI = 39%–68%) versus 31% (95% CI = 18%–49%) for the radiotherapy-alone group (P = .02). The 3-year disease-free survival rate was 42% (95% CI = 30%–57%) for the combined-treatment group versus 20% (95% CI = 10%–33%) for the radiotherapy-alone group (P = .04). Locoregional control of the disease was 66% (95% CI = 51%–78%) for the combined-treatment group versus 42% (95% CI = 31%–56%) for the radiotherapy-alone group (P = .03) (Fig. 2, A and B).

Patterns of Relapse

A tumor recurrence was observed in 65 patients who received radiotherapy alone. The site of the primary tumor was the most common location of recurrence (in 58 patients [89%]). Lymph nodes were involved in 35 patients (54%), and distant metastases were observed in 12 (18%). The percentage of recurrences totals more than 100 because some patients had recurrences at multiple sites.

The tumor recurred in 40 patients after combined therapy, with the most common location being the site of the primary tumor (in 36 [90%] of 40 patients). Lymph node relapse was present in 21 (52%) patients, and distant metastases were present in 12 (30%). The patients' status, patterns of treatment failure, and cause of death are shown in Table 3, B.

Table 3. Effects of treatment by treatment arm

Table 3, A. Acute toxic effects of treatment*

Toxic effect	RT (n = 113)	RT + CT (n = 109)	P†
Mucositis			
Patchy mucositis	32	57	.005
Confluent fibrinous mucositis	7	14	
Skin			
Erythema/pruritis/dry desquamation	47	44	.02
Moist desquamation	12	23	
Nutritional status			
Weight loss >10% of body mass	6	14	.04
Need for feeding tube	15	36	.02
Hematology			
Neutrophil count <0.9 cells/mm^3	0	4	.04
Platelet count <50 cells/mm^3	1	6	.04
Hemoglobin level <8 g/100 mL	0	3	.05
Toxic death	0	1	

Table 3, B. Causes of death and patterns of failure according to treatment group*

Category	RT (n = 113)	RT + CT (n = 109)
Alive at last contact, No. (%)	44 (39)	62 (57)
Dead, No. (%)	69 (61)	47 (43)
Cause of death, No. (%)		
Oropharyngeal cancer	56 (81)	32 (68)
Treatment complication	0	1
Intercurrent disease	9 (13)	9 (19)
Secondary tumor	1	2
Unknown	3	3
Patterns of failure, No. (%)		
Local tumor recurrence	58 (51)	36 (33)
Regional (nodal) recurrence	35 (31)	21 (19)
Distant metastases	12 (11)	12 (11)

Table 3, C. Late toxic effects of treatment*

Toxic effect	RT (n = 113)	RT + CT (n = 109)	P†
Grade 3 or 4 xerostomia	6	10	.1
Severe cervical fibrosis	3	12	.08
Bone necrosis	0	0	
Radiation myelitis	0	0	

*RT = radiotherapy; CT = chemotherapy.

†All P values are two-sided and considered to be statistically significant for P<.05 (chi-squared test).

Late Toxic Effects

With a median follow-up of 35 months, the overall incidence of severe late toxicity (grades 3 and 4) was 9% in the radiotherapy-alone arm and 14% in the combined-treatment group. A trend, the observation of more severe cervical fibrosis in patients who received both chemotherapy and radiation therapy, approached statistical significance. No bone necrosis and radiation myelitis were observed (Table 3, C).

DISCUSSION

We found a significant prolongation of overall and disease-free survival among patients with stages III and IV squamous cell carcinoma of the oropharynx who received concurrent chemotherapy with conventional radiotherapy. This gain was due to

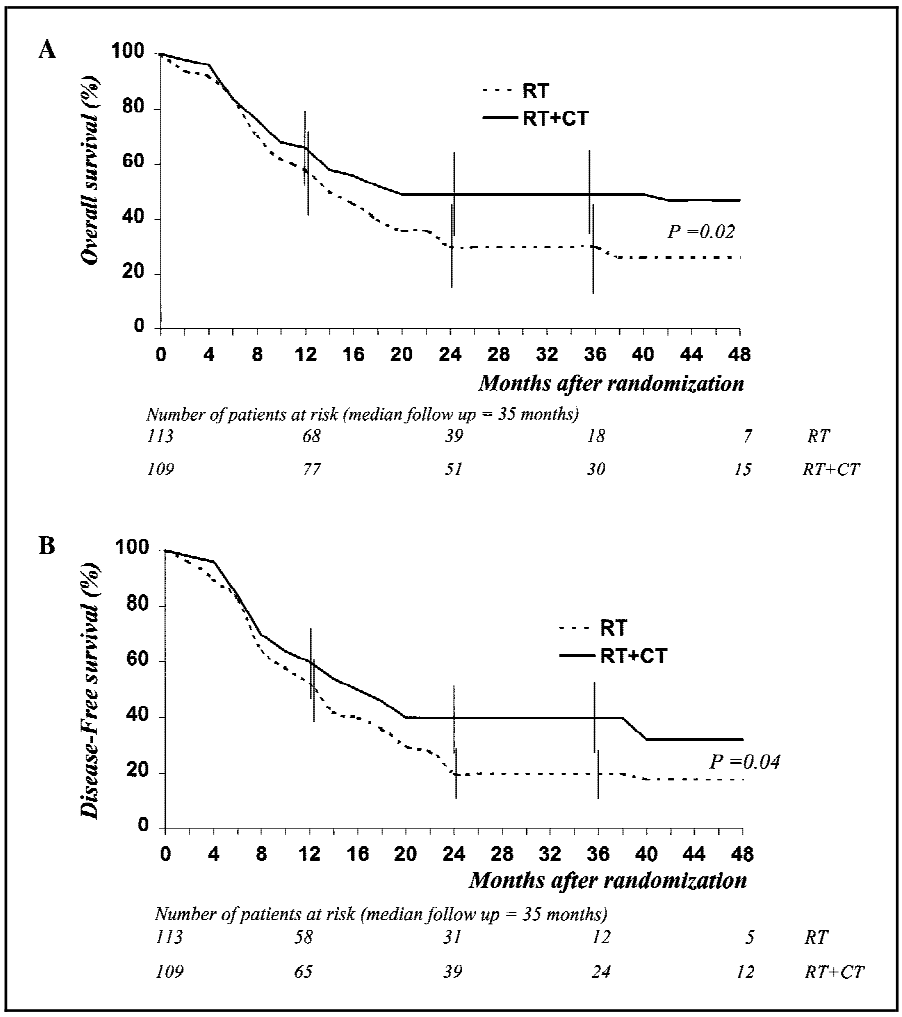

Fig. 2. Survival among patients with oropharyngeal cancer treated with radiotherapy alone (RT) or with radiotherapy with concomitant chemotherapy (RT + CT). **A)** Overall survival as analyzed by the Kaplan–Meier method. Death from any cause was included in the analysis. **B)** Disease-free survival as analyzed by the Kaplan–Meier method. **Error bars** give 95% confidence intervals at representative times after random assignment a treatment arm. **Below each graph** is the total of patients at risk for the same time points. Two-sided *P* values are considered to be statistically significant for .05 (logrank test).

a locoregional control rate improvement and was associated with a statistically significant increase in acute toxicity, especially regarding severe mucositis.

Radiotherapy and chemotherapy may be combined in several ways in treating head and neck cancer. The two treatments may be given simultaneously or in alternation. Radiotherapy may be delivered with a conventional fractionation or with an accelerated or hyperfractionated regimen. Conventionally fractionated radiotherapy with concurrent chemotherapy has been tested in several randomized trials. Early randomized trials used single-agent chemotherapy with bleomycin *(16,17),* methotrexate *(18),* 5-FU *(6),* mitomycin C *(19),* or low-dose cisplatin *(5).* Some of these trials showed statistically significant improvement in local control and/or survival. However, data from these studies remained controversial, and combined treatment with a single agent has not been used as standard therapy for nonresectable advanced disease. The cisplatin–5-FU regimen is one of the most active cytotoxic drug combinations against head and neck carcinoma. It was evaluated with concomitant radiotherapy in a randomized study from the Cleveland Clinic *(20).* Three-year disease-free survival was statistically significantly increased among the patients who received radiotherapy together with chemotherapy rather than radiotherapy alone (67% versus 52%, respectively). The reasons for using carboplatin in our study were as follows: fewer toxic effects on renal function; less nausea and vomiting; the ability to give the drug on an outpatient basis; and the existence of data, suggesting that the regimen has a radiosensitizing effect *(13,21).* The three-arm randomized study by Jeremic et al. *(4)* reported a higher 5-year survival rate when chemotherapy was added to radiation therapy as compared with radiation therapy alone. No differences were observed between cisplatin and carboplatin in that study.

The patient population in our study is homogeneous, with all of the patients diagnosed as having oropharyngeal carcinomas. Most of the earlier studies have enrolled patients with head and neck cancers, including some patients with nasopharynx or paranasal sinus tumors. The natural history, prognostic factors, and radiotherapy technique as used are very different from one tumor site to another. Data regarding treatment toxicity and efficacy will be more accurate in homogeneous groups of patients, and our further studies will each be focused on one selected primary tumor site.

Alternating radiotherapy and chemotherapy is supposed to produce a less acute mucosal reaction, but this regimen may prolong the overall treatment time, with a risk of tumor repopulation that may adversely affect the efficacy of radiotherapy. The trial from Italy's National Institute for Cancer Research *(7,8)* that compared radiotherapy alone with an alternating regimen of chemotherapy and radiotherapy in unresectable carcinoma of the head and neck reported improved 5-year survival rates in the combined-treatment group. However, the poor results in the control arm (5-year disease-free survival rate, 9%) could be explained by a high proportion of patients who experienced prolongation of their overall radiotherapy treatment time and who received a median total dose of only 62 Gy. Further studies are necessary to test the validity of this approach.

On the basis of the apparent advantages of hyperfractionated and/or accelerated radiotherapy when it is used as a single modality *(22,23),* randomized trials have been initiated to compare modified daily fractionation with or without concurrent chemotherapy *(24–26).* The largest study *(24),* performed in Germany, compared hyperfractionated radiotherapy alone or with concomitant chemotherapy with the use of cisplatin, 5-FU, and leucovorin. Three-year survival was 24% versus 48%, respectively, in favor of the combined-treatment group. Another study from the University of North Carolina *(25)* reported similar results by use of an accelerated split-course regimen of radiotherapy. In these two studies, treatment breaks were included in the combined modality arms to reduce the acute toxicity. The study reported by Brizel et al. *(26)* compared continuous-course, ac-

celerated, hyperfractionated radiotherapy versus split-course, hyperfractionated radiotherapy plus concurrent chemotherapy with cisplatin and 5-FU. Survival was increased with the use of chemotherapy and radiation therapy (55% versus 34%, respectively).

Concurrent chemotherapy and radiotherapy appear to be more efficacious than conventional radiotherapy alone. However, some important questions remain unanswered concerning the optimal radiotherapy regimen to combine with chemotherapy. Acute mucosal toxicity is clearly the most important limiting factor, and the ability to reduce this toxic effect will play a significant role in determining the acceptance of this type of treatment.

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