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ORIGINAL REPORT

Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma

Fabrice Denis, Pascal Garaud, Etienne Bardet, Marc Alfonsi, Christian Sire, Thierry Germain, Philippe Bergerot, Beatrix Rhein, Jacques Tortochaux, and Gilles Calais

From the Clinique d'Oncologie et de Radiothérapie, Centre Hospitalier Universitaire, Tours; Centre René Gauducheau, Nantes; Clinique Sainte Catherine, Avignon; Centre Hospitalier, Lorient; Centre Hospitalier Universitaire, Poitiers; Centre Etienne Dolet, Saint-Nazaire; Centre Hospitalier Universitaire, Limoges; Centre Jean Perrin, Clermont-Ferrand, France.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Fabrice Denis, MD, MSc, Clinique d'Oncologie et Radiothérapie, Hôpital Bretonneau, 2 Blvd Tonnelé, 37044 Tours, France; e-mail: fcdenis@club-internet.fr.

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ABSTRACT

Purpose
We report the 5-year survival and late toxicity results of a randomized clinical trial, which showed a 3-year improvement in overall survival and locoregional control of stage III or IV oropharynx carcinoma, using concomitant radiochemotherapy (arm B), compared with standard radiotherapy (arm A).

Patients and Methods
A total of 226 patients were entered onto a phase III multicenter randomized trial comparing radiotherapy alone (70 Gy in 35 fractions; arm A) with concomitant radiochemotherapy (70 Gy in 35 fractions with three cycles of a 4-day regimen comprising carboplatin and fluorouracil; arm B). Prognostic factors were evaluated by univariate and multivariate analysis. Five-year late toxicity was evaluated using National Cancer Institute Common Toxicity Criteria for neurological toxicity, hearing, taste, mandibula, and teeth damage, and Radiation Therapy Oncology Group toxicity criteria for skin, salivary gland, and mucosa.

Results
Five-year overall survival, specific disease-free survival, and locoregional control rates were 22% and 16% (log-rank $P = .05$), 27% and 15% ($P = .01$), and 48% and 25% ($P = .002$), in arm B and arm A, respectively. Stage IV, hemoglobin level lower than 125 g/L, and standard treatment were independent prognostic factors of short survival and locoregional failure by univariate and multivariate analysis. One or more grade 3 to 4 complications occurred in 56% of the patients in arm B, compared with 30% in arm A (*P* was not significant).

Conclusion
Concomitant radiochemotherapy improved overall survival and locoregional control rates and does not statistically increase severe late morbidity. Anemia was the most important prognostic factor for survival in both arms.

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INTRODUCTION

Most oropharyngeal carcinomas are locally advanced at presentation [1]. Patients are therefore often treated using radiation therapy, but the results are poor. In 1994, the French Head and Neck Oncology and Radiotherapy Group (GORTEC) initiated a randomized, phase III, multicenter prospective clinical trial to evaluate the benefit of a concomitant radiochemotherapy (arm B) schedule using a combination of carboplatin and fluorouracil compared with radiation therapy alone (arm A) for advanced-stage oropharynx carcinoma. An improvement in overall survival (OS) at 3 years and locoregional control (LR) rates has been reported [2]. Acute grade 3 and 4 damages were greater in the combined treatment arm, involving skin, mucosa, weight loss, hemoglobin level, and neutrophil count.

We report here the 5-year results of this study. Prognostic factors were evaluated by univariate and a multivariate analysis.

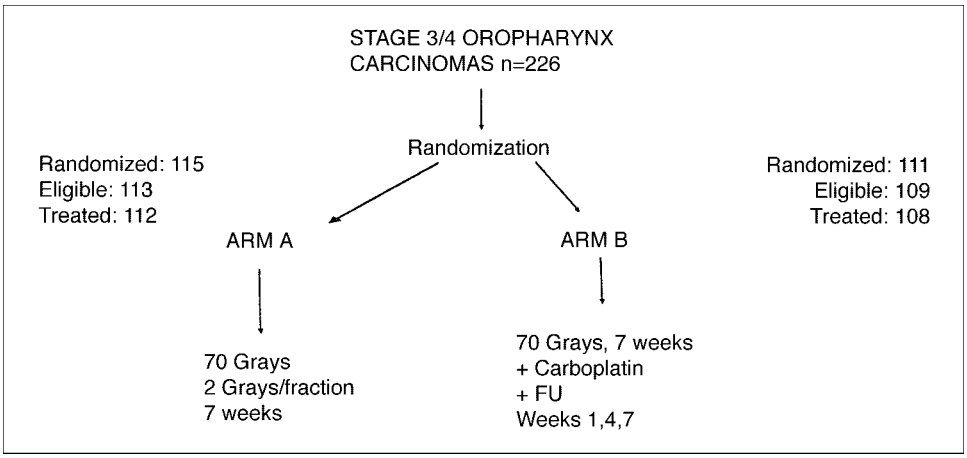

Fig 1. Study design of the randomized trial (arm A: control arm; arm B: combined-modality arm). FU, fluorouracil.

PATIENTS AND METHODS

Study Design

Patients were included in the study if they had invasive squamous cell carcinoma of the oropharynx (stage III or IV, without evidence of distant metastases), were younger than 75 years, and had a Karnofsky performance score of at least 60. Patients were excluded if they had previously undergone specific treatment for this disease (such as neck dissection or primary tumor surgery) 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 1,500 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 regional ethics committee approved the protocol. Written informed consent was obtained from all patients. The study design is shown in Figure 1, and patient characteristics are presented in Table 1.

Treatment

Radiation therapy. All patients in both arms underwent dental care before irradiation (extraction of teeth decaying and/or fluoride protection). The radiotherapy schedule was identical in both arms according to the recommendations of the International Commission on Radiation Units Measurements [3]. Radiation therapy was delivered using cobalt-60 gamma rays, or 4- or 6-MV photons. The oropharynx tumor and upper cervical lymph nodes were treated with two parallel, laterally opposed fields. The median, lower part of the neck, and supraclavicular lymph nodes were treated using a single anterior field with midline blocking. All fields were treated at each session in both treatment arms. The total dose delivered to the primary tumor and involved lymph nodes was 70 Gy (2 Gy per fraction, one fraction per day, and five fractions per week) without any planned interruption. The dose to the spinal cord was kept below 44 Gy.

Chemotherapy. In the experimental arm, patients received three cycles of chemotherapy given concurrently with radiation therapy during the first, fourth, and seventh weeks. Chemotherapy consisted of fluorouracil and carboplatin. Fluorouracil was administered as a 24-hour continuous infusion at a dose of 600 mg/m^2 body-surface area per day for 4 days. Carboplatin was given as a daily bolus of 70 mg/m^2 per day for 4 days. The chemotherapy cycle was started on days 1, 22, and 43.

Follow-Up: Quality Assurance

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 failures of treatment. Only the first failure was reported per patient; subsequent sites of involvement were not recorded. After specific disease recurrence, the patients were treated by the method considered to be most appropriate.

A quality-assurance program was established and undertaken by a team of independent reviewers, consisting of at least one radiation therapist and one radiation physicist. Quality-control procedures for all the patients in the study included a review of the clinical records (endoscopy and computed tomography scan) and all of the radiotherapy records (simulation and control films, and dosimetry). This review was performed.

Late Toxicity

Forty-nine patients were alive at 5.5 years. Two patients in the combined treatment arm did not receive any chemotherapy after randomization, and three were lost to follow-up for the late toxicity assessment but were free of local or distant recurrence (two patients in arm A and one in arm B). Forty-four patients therefore were prospectively evaluated at a single point in time, corresponding to a 5.5-year median follow-up of living patients. The complication rate was determined using the ratio of living patients with one or more adverse events, and patients with and without toxicity at the time of assessment. We used a questionnaire containing 120 items originating from three toxicity scales (National Cancer Institute Common Toxicity Criteria [NCI/CTC]; Radiation Therapy Oncology Group/ European Organization of Research and Treatment of Cancer [RTOG/EORTC] Late Radiation Morbidity Scoring Schema; and the Late Effects on Normal Tissues/Subjective, Objective, Management, and Analytic [LENT/SOMA] scale) to further compare the accuracy and the impact of each classification on grading late effects [4-6].

Adverse events items included symptoms and/or clinical disorders of the following organs or senses: peripheral nerves, hearing, taste, skin, mucosa, bone, teeth, and salivary glands. Because the LENT/SOMA scale was not broadly accepted for routine use in

oncology therapeutic clinical trials, we only report here the late damages rates using the NCI/CTC and RTOG/EORTC scales. Table 2 presents the toxicity scales used to assess late toxicity according to the organs involved.

Items from different scales were mixed inside each category to avoid scale recognition by the clinician. We then transposed fulfilled items on each scale and determined the corresponding grade level (from 0 to 4). Thus, to avoid operator-scoring subjectivity, clinicians did not assess toxicity using grades 0 to 4. The "average grade" was used to determine the grade of an adverse event.

Statistical Analysis

Patients were randomly assigned to a treatment group by a central office after eligibility was established. Random assignment was equilibrated by institution and clinical stage. The two treatments groups were compared for baseline characteristics using the Student's t test for continuous variables and the χ^2 test for category variables. The normal distribution of quantitative variables was verified with the David-Hartley-Pearson test.

Actuarial survival and specific disease-free survival (SDFS) were calculated according to the Kaplan-Meier method and compared with the stratified log-rank test. All reported P values were two-tailed and were considered to be statistically significant for two-tailed $P < .05$. Patients' data were analyzed according to the intention-to-treat principle. No patient was lost to follow-up for assessment of survival and LR. Survival was calculated from the data at random assignment to the most recent follow-up contact or from data of specific disease recurrence or death, and included all patients in the study. In terms of survival, every death (regardless of cause) was considered as a failure. Since all patients were considered to be tumor-free at the end of therapy on the basis of clinical examination and computed tomography scan, SDFS was used; every recurrence (whatever the type) and any deaths before recurrence were considered failures. All patients assigned to the treatment groups were included in all survival analyses.

Prognostic Factors of Survival and LR

Hemoglobin threshold was determined using the receiver-operating characteristic curve to separate patients according to 2-year survival or LR rates [7,8].

A multivariate analysis was carried out using a multiple correspondence analysis (MCA). After checking respect for the necessary conditions of application [9-11], the preliminary descriptive analyses yielded three prognostic parameters describing a six-dimensional space of active modalities for the MCA involving stage III or IV, hemoglobin level lower or greater than 125 g/L, and treatment delivered (irradiation alone or combined radiochemotherapy).

The modalities of the parameters of the 2-year OS (OS $\geq$ 2 years / OS $<$ 2 years), 2-year SDFS (SDFS $\geq$ 2 years / SDFS $<$ 2 years), and 2-year LR (LR $\geq$ 2 years / LR $<$ 2 years) were thrown as passive variables in the inertia of the modalities of the prognostic parameters. Multiple correspondence analysis therefore provided an image of the relative coevolutions of the survival parameters with prognostic parameters in a less-dimensioned space defined by the factorial axis (factors).

In our study, the two first factors maintained a large proportion of the initial variability. The first factorial plan therefore accounts for 74.5% of the inertial variance, with 52.5% for the first factor and 22% for the second factor (Table 3).

In MCA, as in component analyses, the distance of a modality from the center of gravity of the cluster reflects the rarity of the corresponding event in the population. The angle formed by two vectorial directions of modalities illustrates the coincidence (if the angle is acute), the independence (if the angle is close to 90°), or the opposition (if the angle is close to 180°) between the modalities of prognostic parameters studied and the modalities of variables estimating survival or locoregional control.

Computation and graphics of multivariate analysis were performed with two Apple-Macintosh (Cupertino, CA) programs, MMCAul version 4 and GraphMu version 5 [12].

Table 1. Patient Characteristics

Characteristics	Arm A (n = 113)		Arm B (n = 109)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	101		99	
Female	12		10	
Age, years				
Mean	54.4		55.7	
Range	34-74		32-73	
Stage III	35	31	36	33
Stage IV	78	69	73	67
Karnofsky index				
90–100	72	64	58	53
80	25	22	36	33
70	16	14	15	14
Differentiation				
Good	52	46	53	48
Moderate	34	31	24	22
Poor	11	10	14	13
Unknown	16	13	18	17
Tumor location				
Tonsil area	42	37	43	39
Base of the tongue	39	34	40	37
Soft palate	11	10	12	11
Posterior wall	7	6	8	7
Unknown	4		5	
T staging (UICC)				
T1	3	2	5	4
T2	13	12	9	9
T3	58	51	52	48
T4	39	35	42	39
N staging (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

Abbreviation: UICC, Union Internationale Contre Le Cancer.

RESULTS

Survival

After a median follow-up of 5.5 years (range, 4 to 7.2 years), 178 patients had died (96 in arm A and 82 in arm B). The median survival was 13 months in the radiotherapy-alone arm and 20 months in the combined-treatment arm. Patients in arm B had a better 5-year OS rate: 22.4% *v* 15.8% in control

Table 2. Toxicity Scales Used for the Assessment of the Late Effect on Normal Tissues, and 5-Year Grade 3 to 4 Late Toxicity Rates of Combined Treatment Versus Radiation Alone According to the Organs Involved

Organs	Late Toxicity Scales Involved	Percentage of Patients (grade 3 to 4 toxicity)		
		RT (n = 17)	RT + CT (n = 27)	*P*
Neurological toxicity	NCI/CTC	0	0	NS
Taste	NCI/CTC	6	19	NS
Hearing	NCI/CTC	6	0	NS
Mandibula	NCI/CTC	0	6	NS
Teeth	NCI/CTC	12	4	NS
Xerostomia	RTOG/EORTC	18	15	NS
Skin and subcutaneous tissue	RTOG/EORTC	6	7	NS
Mucosa	RTOG/EORTC	18	15	NS

Abbreviations: RT, radiotherapy alone; RT + CT, radiotherapy and chemotherapy (concomitant radiotherapy); NCI/CTC, National Cancer Institute Common Toxicity Criteria; NS, not significant; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

arm ($P = .05$). The 5-year SDFS rate was 26.6% in arm B versus 14.6% in arm A ($P = .01$). Locoregional control of the disease was 47.6% for the combined-treatment group, versus 24.7% for the radiotherapy-alone group ($P = .002$; Figs 2, 3, and 4).

Patterns of Relapse

Locoregional and distant tumor failure (including recurrence or persistent lesion after treatment) was observed in 83 patients who received radiotherapy alone. The site of the primary tumor was the most common location of recurrence (66 patients; ie, 80% of patients with relapse). Lymph nodes were involved for 37 patients (45% of patients with relapse), and distant metastases were observed in 19 patients (23% of patients with relapse). The percentage of locoregional failure totals more than 100 because in some patients, recurrences occurred at more than one site.

Locoregional tumor failure was observed in 62 patients after combined therapy, with the most common location being the site of the primary tumor (in 40 of 62 patients [65%]). Lymph node relapse was observed in 21 patients (34%), and distant metastases were present in 20 patients (32%). Patients' status, patterns of treatment failure, and cause of death are presented in Table 4.

Surgical salvage of locoregional or distant failures was performed in 30 patients (17 in the control arm, 13 in the experimental arm). Two patients were alive at the time of evaluation, and median survival of patients who had undergone surgical salvage was 9.4 months.

Table 3. Expression of the Inertia of the Prognostic Parameters Account for the First Three Factors on Multiple Correspondence Analysis

Factorial Axis (factor)	Factor 1	Factor 2	Factor 3
Proportion of initial variance	0.525	0.220	0.145
Relative contribution of the prognostic variables to the factorial axis			
Treatment delivered	0.224	0.702	0.024
Stage III or IV	0.521	0.187	0.218
Hemoglobin level	0.606	0.025	0.306

Prognostic Analysis

Hemoglobin level before treatment and stage were significant prognostic factors for survival and locoregional control in univariate analysis. However, age, gender, tumor differentiation, and tumor location were not significant factors for survival or locoregional control.

Multivariate analysis showed that the most important factors for short survival (< 2 years after randomization) were low pretreatment hemoglobin level (< 125 g/L), stage IV disease, and radiation therapy alone. A low hemoglobin level was found to be the most negative factor for OS, SDFS, and LR (< 2 years). Probability of death within 2 years in patients with hemoglobin levels less than 125 g/L (37 patients [17%]) was 92% (odds ratio, 10.36; 95% CI, 3.07 to 34.97; $P < .0001$). Patient distribution according to survival and hemoglobin level is shown in Figure 5. A high level of hemoglobin (≥ 125 g/L) was associated with long-term

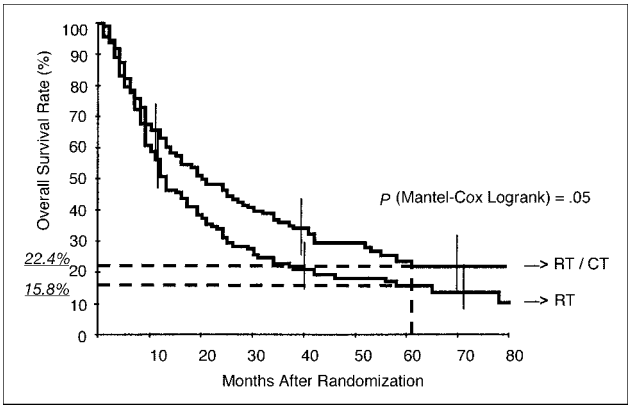

Fig 2. Overall survival among patients with oropharyngeal cancer treated with radiotherapy alone (RT) or with radiotherapy with concomitant chemotherapy (RT/CT) as analyzed by the Kaplan-Meier method. Death from any cause was included in the analysis.

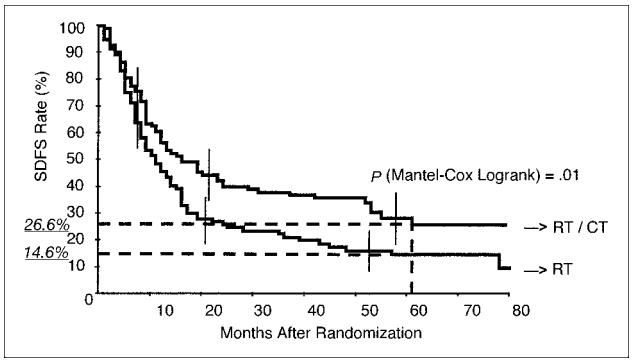

Fig 3. Specific disease-free survival (SDFS) as analyzed by the Kaplan-Meier method. Every recurrence (whatever the type) and any deaths before recurrence were considered to be failures and were included in the analysis. RT, radiotherapy; CT, chemotherapy.

survival (> 2 years) in 48% of patients. Table 5 lists the significant factors for different outcome features on multivariate analyses of the whole series.

Survival and LR were better in patients with stage III than stage IV disease. A low hemoglobin level was more often found in patients with stage IV disease, and a high hemoglobin level was more often found in patients with stage III disease (χ^2 $P = .006$). Stages and hemoglobin level were not dependent on treatment arm.

In the multiple correspondence analysis, the angle in the center formed by the low hemoglobin level parameter and overall early deaths was more acute than the angle formed by the low hemoglobin level parameter and specific (due to cancer or treatment) early deaths. A lower locoregional control was observed in patients with anemia before treatment, leading to lower survival rate, but an improvement in the rate of death of intercurrent-cause deaths was also observed in patients with a low hemoglobin level (Fig 6).

5-Year Late Toxic Effects

Using RTOG/EORTC scale for late effects assessment of mucosa, skin, and salivary glands, and NCI/CTC for neurological, taste, teeth, mandibula, and hearing toxicity assessment, one or more grade 3 to 4 complications occurred in 56% of the patients in arm B, compared with 30% in arm A ($P = .12$). There were no statistical differences between arm A and arm B grade 3 to 4 late effects (Table 2). Grade 4 toxicity was not statistically different between the two arms (2% and 1.2% in arm B and arm A, respectively).

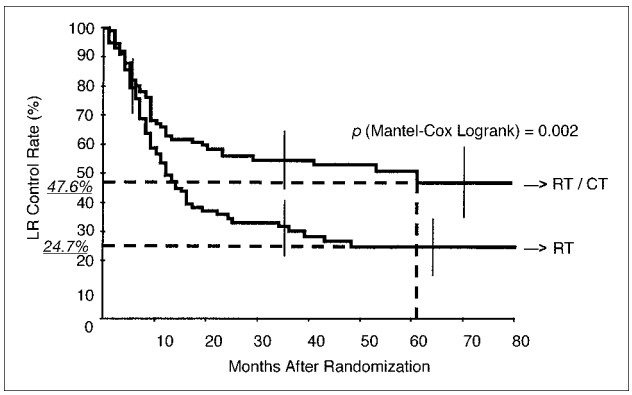

Fig 4. Locoregional control (LR) rate as analyzed by the Kaplan-Meier method. Error bars give 95% CIs at representative times after random assignment to treatment arm. Two-tailed *P* values are considered to be statistically significant for .05 (log-rank test). RT, radiotherapy; CT, chemotherapy.

Table 4. Causes of Death and Patterns of Failure According to Treatment Group

Category	RT (n = 113) No. of Patients	%	RT + CT (n = 109) No. of Patients	%
Alive at last contact	17	15	27	25
Dead	96	85	82	75
Cause of death				
Oropharyngeal cancer	74	65	51	47
Treatment complication	0		1	
Intercurrent specific disease	9	13	15	14
Secondary tumor	4	3	8	7
Unknown	5		5	
Patterns of failure				
Local tumor failure	66	58	45	41
Regional (nodal) failure	37	33	21	19
Distant metastasis	19	17	20	18

Abbreviations: RT, radiotherapy alone; RT + CT, radiotherapy and chemotherapy (concomitant radiotherapy).

DISCUSSION

The 5-year analysis of the data of our study confirms the significant improvement in OS and SDFS rates previously reported among patients with stage III and IV squamous cell carcinoma of the oropharynx who received concomitant radiochemotherapy compared with those treated with radiation therapy alone [2].

This improvement was due to a better locoregional control rate and was statistically associated with a significant increase in acute and severe adverse events. The results of the radiotherapy-alone arm of our multicenter randomized study seem inferior to the vast institutional experience reported by Fein et al [13]. However, in their retrospective study, patients with advanced neck node disease had planned neck dissection after radiotherapy. Survival rates cannot be compared with those reported in our study because of the bias of selection inevitably met in a retrospective study and the absence of similar inclusion criteria between the studies. Such differences may lead to confusion factors that may explain the apparent differences in survival between the former and the present reports.

A recent meta-analysis by Pignon et al [14] suggested that the impact of chemotherapy on OS in head and neck cancer is small but led to an absolute effect on 5-year survival of about

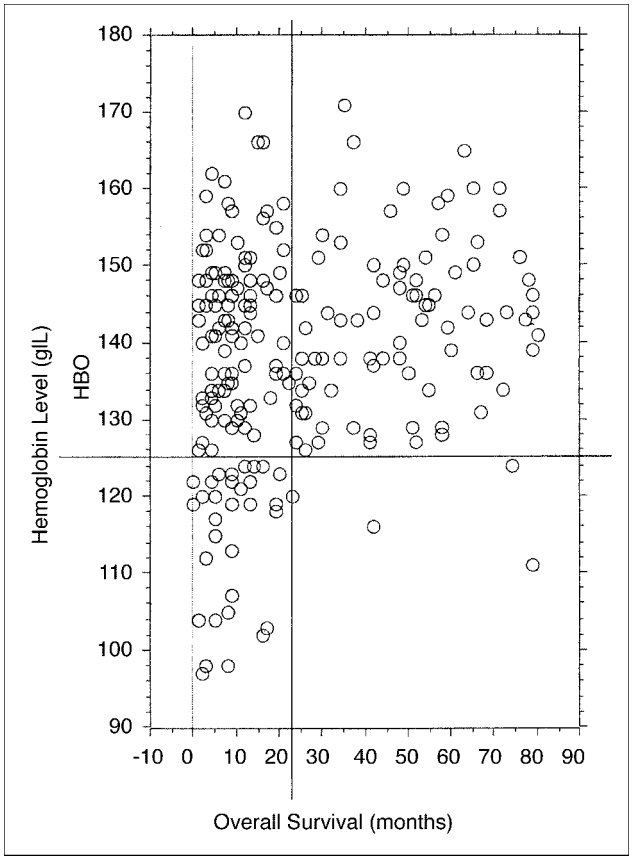

Fig 5. Patient distribution according to survival and hemoglobin level. Each circle represents a patient. HBO, hemoglobin.

10%. Concomitant platin-based chemotherapy used alone [15,16] or in combination with fluorouracil [17] with conventional fractionation led to significant improvement in survival as compared with radiation therapy alone. Carboplatin was chosen in our study to limit adverse effects on renal function and severe nausea. Moreover, carboplatin was shown to be as effective as cisplatin in a randomized study of concurrent radiochemotherapy [16].

Randomized studies of hyperfractionated and/or accelerated radiotherapy used as a single modality have suggested advantages compared with conventional radiotherapy [18]. Modified daily fractionation with concomitant chemotherapy has shown significant improvement of survival in clinical studies [19]. A German multicenter study of hyperfractionated radiotherapy with or without simultaneous chemotherapy using cisplatin and fluorouracil showed an improvement in 3-year survival rate (48% *v* 24%; $P < .003$) with an improvement in locoregional control rate in patients with head and neck carcinomas (36% *v* 17%; $P < .004$) [20]. The locoregional control rate seemed to be similar to the rate reported in our study. However, the radiation therapy was delivered with two scheduled treatment breaks in the German study.

No deaths were caused by late toxicity in our study and we did not observe objective myelitis. Two patients (one in each arm) had distal dysesthesia, without Lhermite's sign, and another in arm B presented with chronic cervical pain. The spinal cord was thus not affected by the concomitant chemotherapy.

In our study, the overall grade 3 to 4 late toxicity rate was not statistically different between both arms using RTOG/EORTC and NCI/CTC scales. However, the NCI/CTC scale was not designed for late effects reporting, and RTOG/EORTC may have underestimate some toxicity because it does not record all the side effects observed [4,23].

However, overall grade 3 to 4 late toxicity rates seemed to be very high in both arms, but data concerned 8 organs or functions, and grade 4 toxicity was relatively rare (2% and 1.2% in arm B and arm A, respectively). Most chemoradiation studies did not assess late toxicity or reported incidence of grade 3 to 4 late effects of 5% to 15% without precision on used tools or did not report toxicity of so many organs [17,19-21]. Late toxicity of our study was assessed using three toxicity scales (RTOG/EORTC, NCI/CTC and LENT/SOMA). We chose to present data for late effect assessment using RTOG/EORTC and NCI/CTC scale because LENT/SOMA was not broadly accepted for routine use in oncology therapeutic clinical trials. However, we conducted a comparison of the three late toxicity tools [4]. Using three scales simultaneously, the transposability of patients symptoms was improved, the number of late effect and the number of patients having one or more grade 3 to 4 late effects was also amplified (82% in arm B and 47% in arm A, with a statistical difference for teeth-related late effects only). These data suggest that higher rate may indeed be a more accurate reflection of the true rate as already suggested by Laszlo et al and Hoeller et al [22,23]. Some patients with a type of adverse event may not be taken into account for late

Table 5. Factors in Multivariate Analyses Affecting Outcome for Patients

	Low Prognostic Factor	Good Prognostic Factor	Overall Survival		Specific Disease-Free Survival		Locoregional Control	
			OR	95% CI	OR	95% CI	OR	95% CI
Hemoglobin level	< 125 g/L	≥ 125 g/L	10.36	3.07 to 34.97	6.06	1.79 to 20.52	7.34	2.17 to 24.84
Stage	IV	III	2.57	1.42 to 4.64	3.19	1.72 to 5.90	2.88	1.58 to 5.26

Abbreviation: OR, odds ratio.

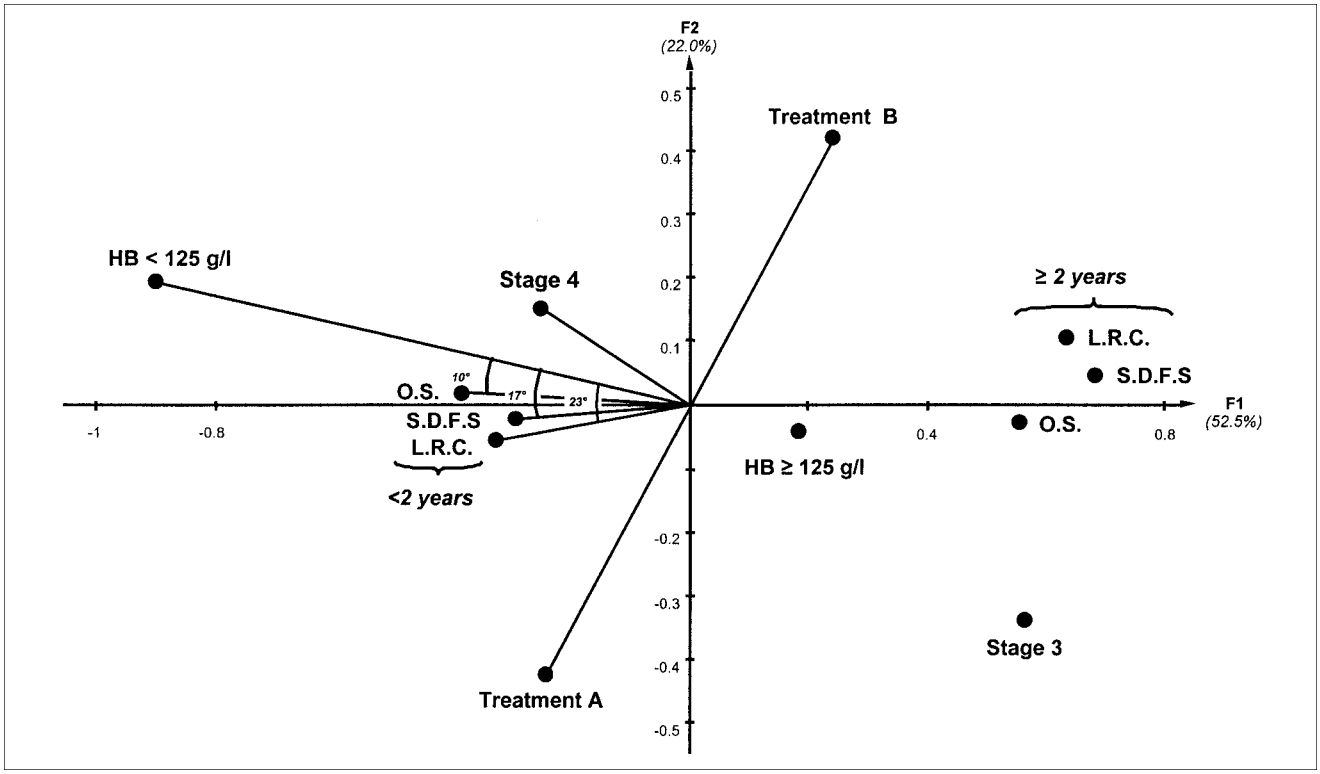

Fig 6. Multivariate analysis assessed by Multiple Correspondence Analysis. The intensity of the association of a prognostic factor and a survival criterion is inversely proportional to the angle formed by both parameters. If an angle is close to 0°, the relation between both parameters is close. HB, hemoglobin level; O.S., overall survival; S.D.F.S., specific disease-free survival; L.R.C., locoregional control; F1, factor 1; F2, factor 2.

toxicity assessment or may have a lower or a higher toxicity grade according to the toxicity scale used.

We did not assess long term impairments of both laryngeal and esophageal function because the prospective assessment of late toxicity in this study was essentially based on a comparison of late toxicity tools. Since laryngeal and esophageal functions can not be exhaustively reported by two late toxicity scales, no comparison of transposability and concordance between scales may have been feasible for this toxicity.

We studied the prognostic value of anemia. Hemoglobin level lower than 125 g/L seemed to be an independent prognostic factor in squamous cell carcinoma of the oropharynx treated with radiation therapy alone or with concurrent chemotherapy. Others studies found similar results [24,25].

In our study, patients with anemia at presentation had a lower 2 year OS, a lower SDFS, and a lower locoregional control rate compared with those who had no anemia. Anemia was almost always associated with a higher probability of death caused by intercurrent specific disease. Some patients presented pretherapeutic anemia probably as a result of the malignant process itself (they more often had stage IV disease). The direct correlation between anemia, tumor hypoxia, and poor response to radiochemotherapy and/or chemotherapy has been clinically proven [26-28].

Recombinant human erythropoietin administration may improve, at least in part, the therapeutic outcome and the patient prognosis. A randomized trial is needed to determine whether raising hemoglobin levels during radiation treatment can overcome the negative impact of anemia. Moreover, better selection of patients with advanced head and neck carcinoma, based on initial hemoglobin level may lead to more appropriate treatment strategies.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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