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ORIGINAL REPORT

Phase III Study Comparing Cisplatin Plus Fluorouracil to Paclitaxel, Cisplatin, and Fluorouracil Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Head and Neck Cancer

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

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ABSTRACT

Purpose
To compare the antitumor activity and toxicity of the two induction chemotherapy treatments of paclitaxel, cisplatin, and fluorouracil (FU; PCF) versus standard cisplatin and FU (CF), both followed by chemoradiotherapy (CRT), in locally advanced head and neck cancer (HNC).

Patients and Methods
Eligibility criteria included biopsy-proven, previously untreated, stage III or IV locally advanced HNC. Patients received either CF (cisplatin 100 mg/m^2 on day 1 plus FU 1,000 mg/m^2 continuous infusion on days 1 through 5) or PCF (paclitaxel 175 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 2, and FU 500 mg/m^2 continuous infusion on days 2 through 6); both regimens were administered for three cycles every 21 days. Patients with complete response (CR) or partial response of greater than 80% in primary tumor received additional CRT (cisplatin 100 mg/m^2 on days 1, 22, and 43 plus 70 Gy).

Results
A total of 382 eligible patients were randomly assigned to CF (n = 193) or PCF (n = 189). The CR rate was 14% in the CF arm *v* 33% in the PCF arm ($P < .001$). Median time to treatment failure was 12 months in the CF arm compared with 20 months in the PCF arm (log-rank test, $P = .006$; Tarone-Ware, $P = .003$). PCF patients had a trend to longer overall survival (OS; 37 months in CF arm *v* 43 months in PCF arm; log-rank test, $P = .06$; Tarone-Ware, $P = .03$). This difference was more evident in patients with unresectable disease (OS: 26 months in CF arm *v* 36 months in PCF arm; log-rank test, $P = .04$; Tarone-Ware, $P = .03$). CF patients had a higher occurrence of grade 2 to 4 mucositis than PCF patients (53% *v* 16%, respectively; $P < .001$).

Conclusion
Induction chemotherapy with PCF was better tolerated and resulted in a higher CR rate than CF. However, new trials that compare induction chemotherapy plus CRT versus CRT alone are needed to better define the role of neoadjuvant treatment.

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INTRODUCTION

Head and neck cancer (HNC) comprises a heterogeneous group of cancers originating at different sites in the upper aerodigestive tract. These tumors share similar epidemiologic characteristics and clinical management strategies. The incidence of newly diagnosed HNC in Europe has been estimated to be 80,000 patients annually.[1] Squamous cell carcinoma (SCC) is the predominant histologic type, accounting for

more than 90% of the cases. Oral cavity and oropharynx are the most frequent sites.[1]

Induction chemotherapy for locally advanced and unresectable HNC has been evaluated in clinical trials for more than two decades without any consistent proof of benefit. However, this strategy is widely used in the community, where more than half of the specialists use induction chemotherapy in their clinical practice.[2] The most commonly used regimen is the combination of cisplatin and fluorouracil (FU; CF), which has become the standard chemotherapy regimen in SCC of the head and neck. To date, several randomized trials have failed to demonstrate a clear superiority of neoadjuvant CF in terms of locoregional tumor control and/or patient overall survival (OS), although a meta-analysis has shown a small but significant benefit in survival.[3] New regimens are continuously being evaluated in the induction setting because this is the most appropriate scenario where the true activity of a drug combination can be optimally assessed.

The taxanes, including paclitaxel, have demonstrated single-agent activity in patients with SCC of the head and neck in several phase II trials.[4-6] In a previous study, we reported a remarkable response rate of 88% for the paclitaxel-cisplatin-FU (PCF) combination as induction chemotherapy without a significant impact in toxicities at the FU recommended dose of 500 mg/m^2/d continuous infusion for 5 days.[7] These results suggest that integrating taxanes in the neoadjuvant setting may lead to increased antitumor effects with tolerable adverse effects.

This multicenter, prospective, randomized, phase III trial was designed to determine the efficacy of a three-drug chemotherapy regimen administered as induction treatment in patients with HNC. The primary objective of the trial was to compare the complete response (CR) rates to induction chemotherapy that could be translated in benefit in survival to select the best neoadjuvant schedule in this set of patients treated with standard chemoradiotherapy (CRT) as radical treatment. Secondary end points included time to treatment failure (TTF), toxicities, organ preservation rate, and OS.

PATIENTS AND METHODS

Patient Population

Patients were enrolled at 15 centers in Spain. Patients were eligible if they had biopsy-proven, previously untreated, stage III or IV SCC of the oral cavity, oropharynx, hypopharynx, or larynx. Patients with T1N1M0 or T2N1M0 or M1 (metastatic disease) disease were ineligible. Other eligibility criteria included measurable disease and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1. Patients also had to have normal organ functions as defined by an absolute neutrophil count $\geq$ 1,500 cells/μL, platelet count $\geq$ 100,000 cells/μL, total bilirubin less than 1.25$\times$ the laboratory upper limit of normal, and a calculated creatinine clearance of more than 50 mL/min.

Pretreatment staging involving ears, nose, and throat examination and computed tomography (CT) scanning of the primary tumor site and the neck were performed and evaluated by members of a committee with expertise in the management of HNC. Tumor evaluations were performed at several time points, including within a period of no more than 3 weeks before study entry and at the completion of induction therapy and CRT or at the time of treatment termination if patients where prematurely withdrawn from the study. When there was a discrepancy in the evaluation assessed by the two methods of tumor evaluation, the more conservative result was reported. Imaging was also performed whenever clinically indicated to rule out metastatic disease.

Patients were stratified according to center, disease location (larynx *v* hypopharynx *v* oropharynx *v* oral cavity), ECOG PS (0 *v* 1), and resectability (yes *v* no). The random assignment was centralized, and Zelen's method was used to achieve balance in treatment assignments among the participating institutions.[8]

Patients were required to provide written informed consent before inclusion in the study. The study protocol was approved by the institutional review board at each study center, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Treatment Plan

The study design algorithm is depicted in Figure 1.

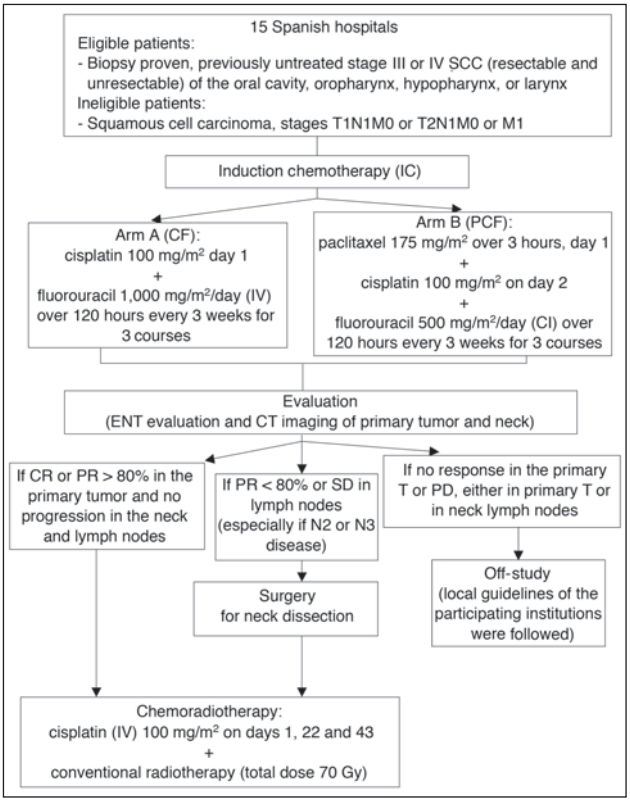

Fig 1. Study design algorithm. SCC, squamous cell carcinoma; CF, cisplatin and fluorouracil; PCF, paclitaxel, cisplatin, and fluorouracil; IV, intravenous; CI, continuous intravenous infusion; ENT, ears, nose, and throat; CT, computed tomography; CR, complete response; PR, partial response; PD, progressive disease; T, tumor; SD, stable disease.

Induction chemotherapy. The treatment schedule for arm A (CF) was as follows. Cisplatin was administered intravenously at a dose of 100 mg/m^2 on day 1, and FU was administered at a dose of 1,000 mg/m^2/d by continuous intravenous infusion on days 1 to 5 every 3 weeks for three courses.

The treatment schedule for arm B (PCF) was as follows. Paclitaxel 175 mg/m^2 was administered over 3 hours on day 1. Cisplatin was administered intravenously at a dose of 100 mg/m^2 on day 2, and FU was administered at a dose of 500 mg/m^2/d by continuous intravenous infusion on days 2 to 6 every 3 weeks for three courses.

On day 22, the requirements in both arms to allow retreatment of the patients were as follows: absolute neutrophil count more than 1.5×10^9/L, platelet count more than 100×10^9/L, creatinine clearance more than 50 mL/min, and resolution of all other nonhematologic toxicities (except alopecia and fatigue) to baseline or less than grade 1. If there was a delay of subsequent cycles beyond day 35, the patient was removed from study. The doses of all drugs were reduced after any episode of febrile neutropenia, grade 4 neutropenia lasting more than 5 days, or grade 4 thrombocytopenia. The dose of FU alone was reduced by 25% for patients who developed grade 3 to 4 mucositis or grade 4 anemia or diarrhea. Paclitaxel and cisplatin were reduced by 15% and 25%, respectively, after persistent grade 2 or greater neurosensorial toxicity. Standard intravenous premedications with dexamethasone, diphenhydramine, and cimetidine or ranitidine were administered 30 minutes before paclitaxel infusion to prevent hypersensitivity reactions.

After induction chemotherapy, patients underwent ears, nose, and throat examination and CT imaging of primary tumor and neck. The criteria for response were based on cross-sectional diameter and tumor response, nodal response, and overall response (OR; tumor plus nodal response; WHO criteria). If these examinations identified a CR or partial response (PR) of more than 80% in the primary tumor and no progression in the neck lymph nodes, the patient was offered CRT as part of the protocol treatment. Patients with a PR of less than 80% or stable disease in the neck lymph nodes (especially if N2 or N3 disease) after induction CT were referred to surgery for neck dissection, if the surgeons were in agreement, before the administration of CRT. Patients with no response in the primary tumor or progressive disease either in the primary tumor or in the neck lymph nodes were taken off study or treated according to the individual preference of the investigator.

CRT. Intravenous cisplatin at a dose of 100 mg/m^2 on days 1, 22, and 43 was administered concomitantly with conventional radiotherapy to the primary tumor and to the clinically positive nodes at a total dose of 70 Gy. Radiotherapy was administered in 35 fractions of 2 Gy each over a 7-week period. Nodal areas not clinically involved by tumor received a total dose of 50 Gy. The dose to the clinically positive nodes was supplemented by the radiation directed at the primary tumor or with tangential anterior-posterior beams. Doses and schedules were identical in both treatment arms of the study.

Surgery. Whenever feasible, surgery was recommended to all patients who had a response of less than 80%, stable disease, or progressive disease in the primary tumor and/or progressive disease in lymph nodes. Functional surgery (without loss of organ function such as tonsillectomy and supraglottic laryngectomy) was mandatory whenever possible. In other cases, radical surgery was indicated (for example, total laryngectomy, total glossectomy, or pharyngolaryngectomy). If surgery was not feasible, the treatment choice was left up to the investigator's discretion and within local guidelines of the participating institution, where CRT or radiotherapy was recommended.

Follow-up on completion of treatment. Once treatment was completed, patients were observed for evaluation of disease status and late-onset toxicity every 3 months until disease progression and/or death.

Outcomes

The primary end point of the study was to compare the overall CR rate between the two induction treatment arms to define the best schedule of induction chemotherapy. Secondary end points included TTF, OS, organ preservation rate, and toxicity.

TTF was defined, for the whole population, as the time from random assignment until progression/relapse, second tumor appearance, or removal from protocol as a result of toxicity or death from any cause, including toxicity. OS was measured from the day of random assignment until death, last revision, or loss to follow-up. Organ preservation rate was defined as the percentage of patients with resectable tumors who did not undergo radical surgery in the primary tumor. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (version 1.0) during induction chemotherapy and according to the Radiation Therapy Oncology Group toxicity criteria during CRT treatment.[9] Time to radical surgery was defined as the period of time between the date the therapy was finished until the date the surgery was performed or date of local recurrence or disease related-death when surgery was not feasible.

Statistical Analysis

The study was designed to test whether one of the two induction chemotherapy treatments resulted in a higher CR rate. The expected CR rates after CF and PCF treatments were 40% and 55%, respectively. The sample size was calculated to detect a difference of 15% with an 80% power ($\beta = .2$) and a two-sided significance level of $\alpha = .05$. Therefore, 346 assessable patients were needed. With an expected nonassessable rate of 10%, 380 patients were to be randomly assigned. This sample size was also considered sufficient to detect an increase of 15% in the 3-year survival rate (from 50% to 65%) in the experimental arm with a power of 85% and a two-sided significance level of $\alpha = .05$.

Patient characteristics, toxicity, and response rates in the two treatment arms were compared using the Student's t test for continuous variables and the χ^2 test for categoric variables. Fisher's exact test or Yates correction were used when appropriate.[10] Gaussian distribution of the variables was verified using the Kolmogorov-Smirnov test.[11] All reported P values were two sided, and $P < .05$ was considered statistically significant. Actuarial survival and TTF were calculated according to the Kaplan-Meier method and compared with the log-rank test, as stated in the original study protocol.[12] Once generated, the Tarone-Ware test was applied to the curves. This test takes into account all the events in each time point, and it is appropriate for this heterogeneous population of HNC patients characterized by a nonuniform hazard ratio of events in the follow-up.[13] In the survival analysis, death from any cause was considered as an event.

RESULTS

Patients

Between December 1998 and 2001, 387 patients were randomly assigned to one of two induction treatment arms. Five patients were considered ineligible (one patient with a nasopharyngeal tumor, three patients with metastatic disease, and one patient who withdrew consent before treatment commenced). Thus, data from 382 patients were included in the analysis. Overall baseline characteristics of the study population are listed in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (N = 382)

Characteristics	% of Patients	
	CF (n = 193)	PCF (n = 189)
Sex		
Male	94	94
Female	6	6
Age, years		
Range	37-74	31-75
Median	55	56
Tumor site		
Oral cavity	13	13
Oropharynx	35	34
Pharynx	21	23
Larynx	31	30
ECOG PS		
0	20	14
1	80	86
Resectable		
Yes	34	36
No	66	64
Disease stage		
III	17	15
IV	83	85
TNM stage		
T1N0	0	0
T2N0	0	0
T3N0	8.8	9
T4N0	8.3*	15.3
T1N1	0	0
T2N1	0	0.5
T3N1	7.8	5.8
T4N1	12.4	12.2
T1N2	0.5	0
T2N2	7.8	4.8
T3N2	15.5	15.9
T4N2	23.8	24.9
T1N3	1	1.1
T2N3	2.1	3.2
T3N3	3.6	2.1
T4N3	8.3	5.3

Abbreviations: CF, cisplatin and fluorouracil; PCF, paclitaxel, cisplatin, and fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status.
*$P < .032$.

Compliance

Induction chemotherapy. Patients in arm A received a total number of 534 cycles of induction treatment compared with 542 cycles in arm B. The median number of cycles was three in both treatment arms. The percentage of delayed cycles was significantly higher in arm A than in arm B (27% *v* 12%, respectively; $P < .001$). Cisplatin dose reductions were also significantly higher in arm A than in arm B (9% *v* 5%, respectively; $P < .02$). Dose-intensity in arm A was 81% for cisplatin and 91% for FU; in arm B, dose-intensity was 91% for cisplatin, 98% for FU, and 99% for paclitaxel. Both arm A and arm B differences were statistically significant ($P < .001$).

CRT treatment. Median duration of CRT was 6 weeks in both treatment arms (range, 0 to 8.4 weeks). Median time between completion of induction therapy and CRT commencement was 3.1 and 3.2 weeks in arms A and B, respectively. The median total dose of radiation therapy was 68 Gy in arm A (range, 30 to 76 Gy) and 68 Gy in arm B (range, 30 to 74 Gy), and the median number of cycles of cisplatin combined with radiotherapy was three in both treatment arms (range, one to three cycles).

Efficacy

The treatment outcomes algorithm is depicted in Figure 2.

Induction treatment. Patients randomly assigned to arm B achieved a significantly higher CR rate compared with patients in arm A (14%; 95% CI, 8.7% to 18.0%; *v* 33%; 95% CI, 26.6% to 40.0%, respectively; $P < .001$). The PR rate was similar between the two treatment arms, but the difference in OR rate reached statistical significance. Response rates are listed in Table 2.

Differences between the two treatment arms in terms of CR and OR were observed in populations of patients with resectable and unresectable disease. In patients with resectable disease, CR and OR rates were 15% (95% CI, 6.5% to 23.0%) and 71% (95% CI, 60.4% to 82.2%), respectively, in arm A, and 35% (95% CI, 28.5% to 42.1%; $P < .007$) and 87% (95% CI, 78.8% to 94.8%; $P < .03$), respectively, in arm B.

The CR rates were significantly different between the two treatment arms with respect to primary tumor (33%; 95% CI, 26% to 39% in arm A *v* 49%; 95% CI, 42% to 56% in arm B; $P < .001$) and nodal stage (14%; 95% CI, 9% to 18% in arm A *v* 26%; 95% CI, 20% to 32% in arm B; $P < .002$). A total of 28 patients (19 patients in arm A and nine in arm B) were not assessable for response (12 patients because of toxicity, 13 patients because of early death, and three patients opted to discontinue treatment).

In a multivariate analysis, the three main predictive factors for CR were treatment, disease stage at random assignment, and PS. Treatment arm was the most important prognostic factor for response (odds ratio = 2.47; 95% CI, 1.61 to 3.79; $P < .001$; Table 3).

A blinded radiologic review was performed in 217 patients for whom images were available. On the basis of this

Table 2. Overall Response to Induction Treatment and Chemoradiotherapy

Response	CF			PCF			*P*
	No. of Patients	%	95% CI (%)	No. of Patients	%	95% CI (%)	
Induction treatment							
Complete response	26	14	9.10 to 18.89	63	33	26.30 to 39.70	< .001
Partial response	105	54	46.97 to 61.03	89	47	39.88 to 54.12	
Overall response	131	68	61.42 to 74.58	152	80	74.30 to 85.70	< .001
Stable disease	27	14	9.10 to 18.89	20	11	6.54 to 15.46	
Disease progression	16	8	4.17 to 11.83	8	4	1.21 to 6.79	
Nonassessable	19	10	5.77 to 14.23	9	5	1.89 to 8.11	
Induction and chemoradiotherapy treatment							
Complete response	59	78	68.92 to 87.08	101	88	79.66 to 92.34	NS
Partial response	8	10	3.43 to 16.57	11	10	4.52 to 15.48	NS
Overall response	67	88	80.88 to 95.12	112	98	92.42 to 99.58	NS
Nonassessable	7	9	2.73 to 15.27	2	0.8	0.00 to 2.43	NS

Abbreviations: CF, cisplatin and fluorouracil; PCF, paclitaxel, cisplatin, and fluorouracil; NS, not significant.

blinded review, 45% of patients in arm A had CR in the primary tumor compared with 53% of patients in arm B. For the same patient subgroup, the clinical (including physical examination and panendoscopy) and radiologic assessment performed by the investigators showed a CR rate of 43% in arm A compared with 49% in arm B in primary tumor. Cohen's kappa concordance index[14] for the response in the primary tumor was 0.309 in arm A and 0.244 in arm B, with a $P < .001$. This index indicates that there were no significant differences between the investigators' and the independent reviewers' assessments (ie, no basis of conscious or unconscious bias in the assessments).

One hundred three patients underwent functional surgery or biopsies of primary tumors for pathologic evaluation according to each individual institution's guidelines and procedure preferences; however, this was not a mandatory procedure included in the protocol, and most of the pathologic evaluations were conducted in two hospitals. The most frequent surgical procedures included tonsillectomies, supraglottic laryngectomies, and multiple biopsies in oropharynx and pharynx. Twenty-three percent of patients (95% CI, 12.0% to 34.0%) in arm A and 42% of patients (95% CI, 27.9% to 56.1%) in arm B achieved a pathologic CR at the primary tumor site ($P = .036$).

Table 3. Multivariate Analysis for Response

Factor	OR	95% CI	*P*
Treatment: PCF *v* CF	2.47	1.61 to 3.79	< .001
Stage: III *v* IV	2.24	1.22 to 4.01	.009
ECOG PS: 0 *v* 1	1.54	0.93 to 2.56	.096

Abbreviations: OR, odds ratio; PCF, paclitaxel, cisplatin, and fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status.

CRT treatment. Although 95 patients in arm A and 129 patients in arm B achieved a CR or a PR of more than 80% in the primary tumor, only 76 and 114 patients received CRT as established per protocol, respectively. Of the 190 patients who received the protocol-established CRT, 78% and 10% achieved a CR and PR, respectively, in arm A (OR rate, 88%) compared with 88% and 10% of patients, respectively, in arm B (OR rate, 98%). These figures include patients who did not achieve a CR after induction chemotherapy but did achieve a CR after CRT. As shown in Table 2, the number of CRs after CRT was similar in both groups. Only eight patients were considered nonassessable after CRT (seven patients in arm A and one patient in arm B) as a result of toxicity (one patient in arm A), early death (three patients in arm A), patient refusal (one patient in arm A) and loss to follow-up (three patients: two in arm A and one in arm B; Fig 2).

Surgery. Of those patients with resectable disease at study entry (n = 134; 34% in CF group and 36% in PCF group), 27% underwent radical surgery (mostly laryngectomies) on primary tumor in arm A compared with 12% in arm B ($P < .05$). The majority of these radical surgeries were a result of lack of either CR or major response to induction chemotherapy. However, the decision to proceed with radical surgery was left to the discretion of the attending surgeon at each site and was not specified in the protocol. In addition, salvage surgery after the relapse was performed only in 3% of patients in arm B. This very low number of salvage surgeries was a result of the fact that local recurrences were, in general, bulky locoregional relapses in the majority of patients who were not amenable to surgical resection.

Whenever possible, biopsy and functional surgery, such as supraglottic laryngectomy or hemoglossectomy, were considered as an alternative. The functional surgery

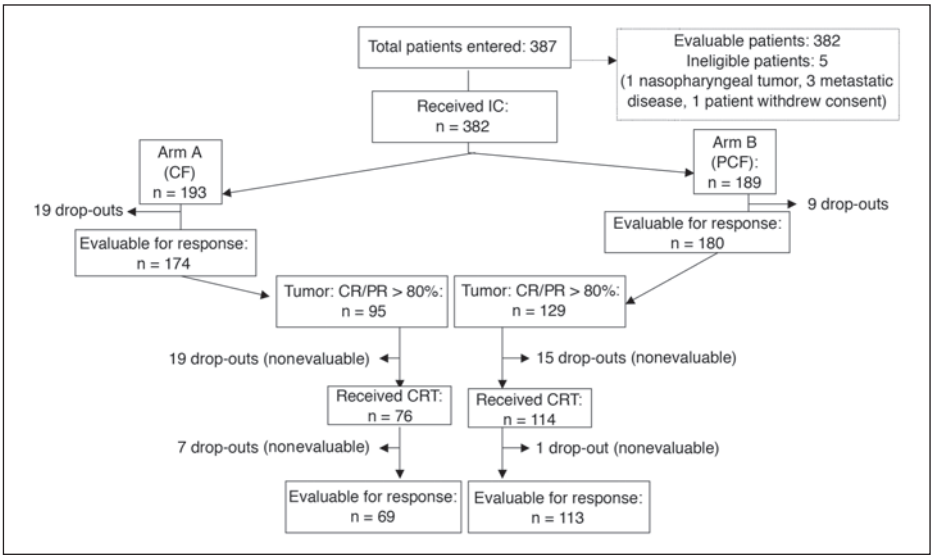

Fig 2. Treatments outcomes algorithm. IC, induction chemotherapy; CF, cisplatin and fluorouracil; PCF, paclitaxel, cisplatin, and fluorouracil; CR, complete response; PR, partial response; CRT, chemoradiotherapy.

rate in arm A was 11% compared with 18% in arm B. Time to radical surgery is represented in Figure 3.

Off-protocol treatment. Of the 193 patients treated in arm A, 95 were treated off protocol because of no major response to chemotherapy. Surgery on primary tumor was performed in 33% of these patients, whereas 50% received radiotherapy or CRT according to the individual guidelines of each participating center. For these patients, the relapse rate was 63%.

Of the 189 patients treated in arm B, 56 were treated off protocol because of lack of complete or major response. Surgery on primary tumor was performed in 50% of the patients, whereas 52% of patients received radiotherapy or CRT. For these patients, the relapse rate was 55%.

Survival outcome. Median follow-up time was 23.2 months (range, 0.3 to 60.3 months) for the overall patient population. The 2-year OS rate was 61.5% (53.64% in arm A *v* 66.5% in arm B). TTF and OS are presented in Figures 4 and 5, respectively. The difference between the treatment arms was more evident in patients with unresectable disease (Figs 6 and 7). A multivariate Cox proportional hazards model is presented in Table 4.

Relapse patterns. With a median follow-up of 23 months, there have been 175 patients with disease progression/

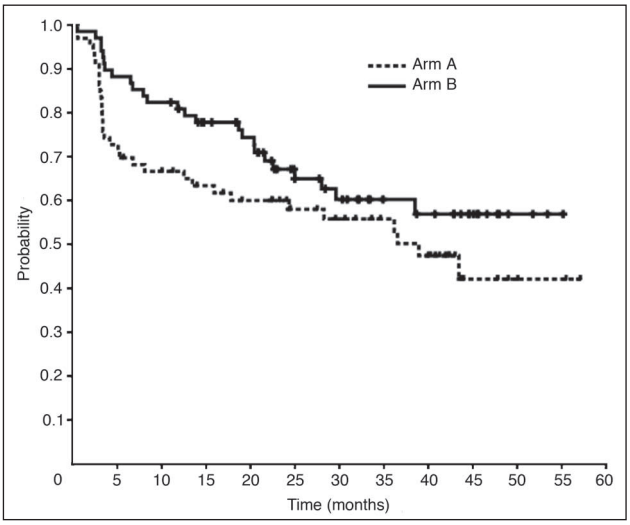

Fig 3. Time lapse between random assignment and radical surgery in patients with resectable tumors (n = 134; arm A, cisplatin and fluorouracil, n = 66: 32 events, 48%; arm B, paclitaxel, cisplatin, and fluorouracil, n = 68: 25 events, 37%; Gray test, $P = .049$).

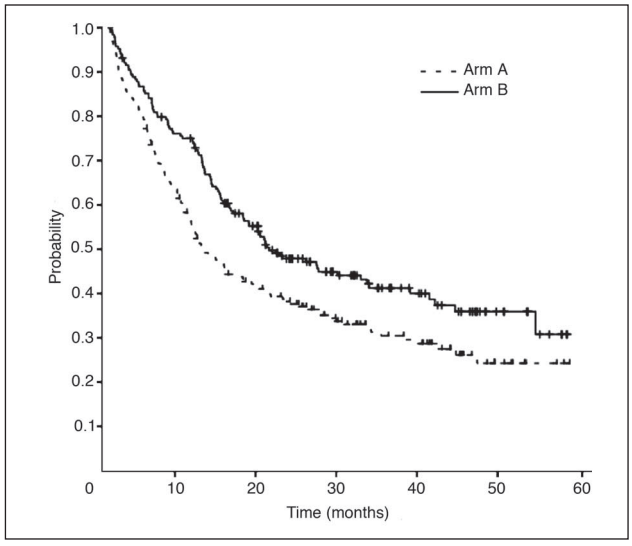

Fig 4. Time to treatment failure (TTF) for all patients (arm A, cisplatin and fluorouracil, n = 193: 133 events, 66%; arm B, paclitaxel, cisplatin and fluorouracil, n = 189: 108 events, 57%; log-rank test, $P = .0062$; Tarone-Ware, $P = .0031$; median TTF: arm A, 12 months [range, 8.6 to 14.5 months]; arm B, 20 months [range, 13.8 to 25.9 months]).

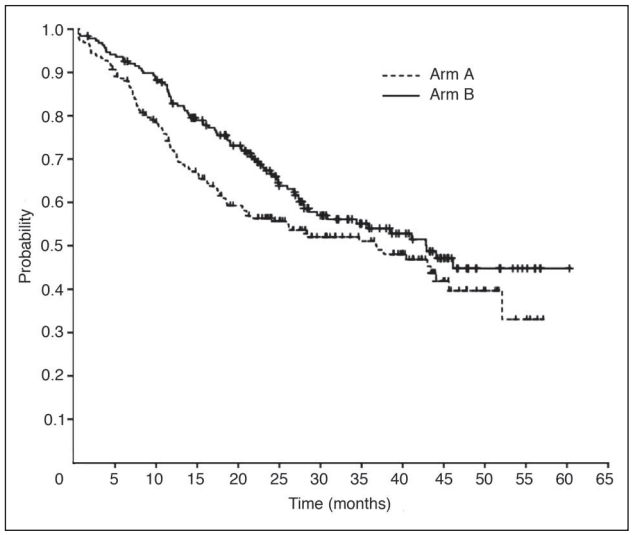

Fig 5. Overall survival (OS) for all patients (arm A, cisplatin and fluorouracil, n = 193: 97 events, 51%; arm B, paclitaxel, cisplatin and fluorouracil, n = 189: 81 events, 43%; log-rank test, $P = .063$; Tarone-Ware, $P = .031$; median OS: arm A, 36.8 months [range, 24.5 to 49.1 months]; arm B, 42.9 months [range, 32.9 to 52.9 months]).

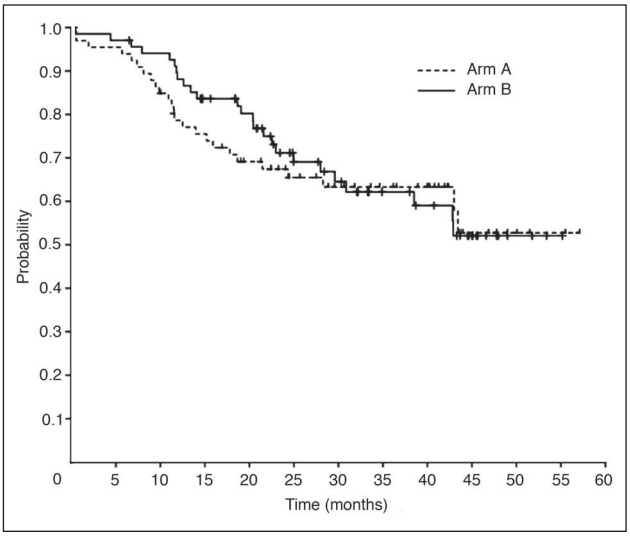

Fig 7. Overall survival (OS) for patients with resectable disease (arm A, cisplatin and fluorouracil, n = 66: 25 events; arm B, paclitaxel, cisplatin and fluorouracil, n = 68: 25 events; log-rank test, $P = .704$; Tarone-Ware, $P = .517$; median OS: the median OS has not been reached for either arm).

relapse (94 in arm A and 81 in arm B). Of these patients, 73% experienced locoregional relapse, and only 14% had distant relapses. For other patients, the site of recurrence was unknown. The frequency and the type of relapse (locoregional and distant) were similar between the two treatment arms.

Second tumors. There were 25 second tumors diagnosed; nine were in arm A (six non–small-cell lung cancers, one breast cancer, and two esophageal cancers), and 16 were in arm B (four non–small-cell lung cancer, six HNCs, one hematologic malignancy, one brain tumor, two esophageal cancers, and one colorectal cancer). The differences were not statistically significant. However, it was difficult to interpret the difference between second primary HNC and locoregional relapse, and probably, as it has been previously reported, some relapses could actually be second primary tumors.

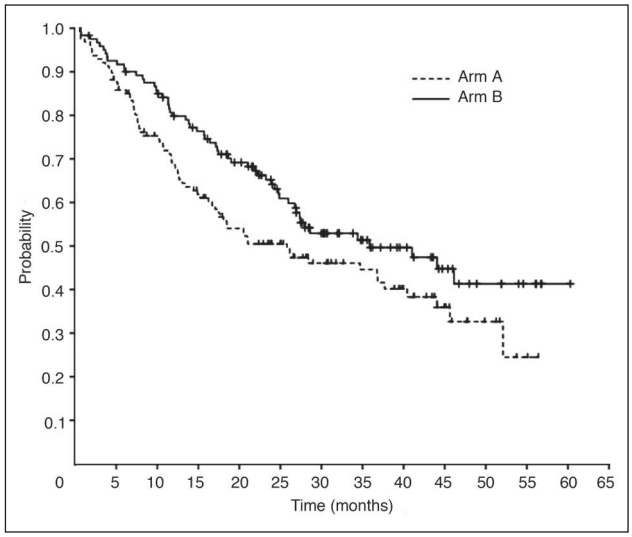

Fig 6. Overall survival (OS) for patients with unresectable disease (arm A, cisplatin and fluorouracil, n = 127: 72 events, 57%; arm B, paclitaxel, cisplatin and fluorouracil, n = 121: 56 events, 46%; log-rank test, $P = .046$; Tarone-Ware, $P = .033$; median OS: arm A, 25.8 months [range, 12.4 to 39.2 months]; arm B, 35.9 months [range, 20.0 to 51.7 months]).

Toxicity

Induction chemotherapy. Grade 3 or 4 acute toxicities observed in the course of the study are listed in Table 5. Twelve patients discontinued the induction treatment before tumor evaluation because of toxicity (eight patients in arm A: three nephrotoxicities, two mucositis, two cardiac toxicities, and one peripheral ischemia; and four patients in arm B: two nephrotoxicities and two cardiotoxicities). Additionally, there were 12 toxic deaths (eight patients in arm A: four patients with myelosuppression and sepsis, one patient with myelosuppression and renal failure, two patients with mucositis at home after temporary discharge from hospital during the nadir period, and one patient with

Table 4. Multivariate Cox Proportional Hazards Model for Survival

Factor	HR	95% CI	*P*
Stage: III *v* IV	1.92	1.15 to 3.21	.013
ECOG PS: 0 *v* 1	1.53	1.02 to 2.30	.040
Resectability: resectable *v* unresectable	1.45	1.03 to 2.03	.031
Treatment: PCF *v* CF	1.33	1.01 to 1.83	.035

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; PCF, paclitaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil.

Table 5. Grade 3 or 4 Acute Toxicity From Chemotherapy (NCI CTC version 1.0) and Chemoradiotherapy (RTOG)

Toxicity	% of Patients CF	% of Patients PCF	*P*
During chemotherapy, n = 382			
Neutropenia	36	37	
Febrile neutropenia	5	8	
Mucositis, grade 2 to 4	53	16	< .001
Diarrhea, grade 2 to 4	13	16	
Nausea/vomiting	8	6	
Alopecia	2	10	< .001
Fatigue	6	3	
Peripheral neuropathy, grade 2 to 4	3	8	
Renal	2	2	
All grade 3 to 4 events	68	60	
Toxic deaths	4	2	
During chemoradiotherapy, n = 190			
Neutropenia	20	32	.054
Febrile neutropenia	4	0	
Mucositis	55	34	.004
Nausea/vomiting	17	4	.003
Fatigue	8	10	
Peripheral neuropathy, grade 2 to 4	11	17	
All grade 3 to 4 events	86	83	
Toxic deaths	2	0.5	

Abbreviations: NCI CTC, National Cancer Institute Common Toxicity Criteria; RTOG, Radiation Therapy Oncology Group; CF, cisplatin and fluorouracil; PCF, paclitaxel, cisplatin, and fluorouracil.

acute myocardial infarction; and four patients in arm B: one patient with myelosuppression and sepsis, two patients with myelosuppression and renal failure, and one patient with neutropenia and depressive syndrome).

CRT. Severe acute toxicities during CRT are listed in Table 5. There were five toxic deaths (four in arm A: one patient with myelosuppression and sepsis, one patient with renal failure because of cisplatin accidental overdosing, one patient with massive upper digestive tract hemorrhage, and one patients infection with *Candida* spp; and one in arm B: massive hemoptysis in a patient with laryngeal necrosis). The total grade 3 or 4 toxicity was the same between the two treatment arms.

DISCUSSION

Induction chemotherapy with CF in patients with HNC has been studied for more than two decades. This study is the first large randomized trial testing the hypothesis that the addition of paclitaxel, an agent with known activity in this disease, to the standard CF regimen results in superior antitumor activity. The PCF regimen significantly improved the CR rate and OR in T and N stage HNC when compared with CF alone in a comparable group of patients with poor prognostic features such as stage IV disease (84%), unresectable tumors (65%), and oropharynx primary tumors (35%).[15]

Although concomitant CRT with cisplatin is currently considered as standard treatment in patients with resectable laryngeal cancers,[16] the optimal treatment strategy remains unclear for patients with other primary tumor sites and patients with unresectable tumors. Likewise, randomized clinical trials have shown the superiority of CRT over radiotherapy alone in oropharynx tumor.[17,18] However, no randomized study comparing induction chemotherapy plus CRT versus CRT alone has been conducted so far. The aim of this study was to define the best neoadjuvant treatment regimen for future comparisons with CRT alone. The results show that PCF is an active regimen in this setting with a favorable toxicity profile, suggesting that induction PCF followed by CRT is an appropriate regimen to test in such studies.

The toxicity profile of the two treatment arms was similar, but mucositis was significantly worse in patients receiving the CF regimen compared with patients receiving the PCF regimen. We have previously reported that the recommended dose of FU in the PCF regimen should be 500 mg/m^2/d for 5 days.[7] In this study, patients receiving CF treatment had a higher number of cycles delayed ($P < .001$) as a result of mucositis and a lower administered dose-intensity of cisplatin and FU ($P < .001$). The major incidence of mucositis during induction chemotherapy and CRT was likely a result of the high dose of FU used in those patients receiving the CF regimen, who experienced a recall effect during CRT. However, the time to initiation of CRT, dose of cisplatin plus radiotherapy, and CR after this treatment were similar between the two arms.

Patients in both treatment arms had lower response rates compared with other trials using similar treatment schedules probably because, in this study, all patients had rigorous assessments using endoscopy and CT scans and, when a discrepancy existed, the more conservative assessment was used. It is important to emphasize that the radiologic assessment of the independent (blinded) reviewer matched the investigator's evaluation.[3,7,15] Differences in CR rates were observed between the two treatment arms (14% in CF arm *v* 33% in PCF arm, $P < .001$), regardless of tumor resectability, primary site, or nodal stage. Previous reports have indicated that patients with CR and with pathologic response to induction chemotherapy have better survival than patients with response to treatment that was less than CR.[19,20] In our trial, pathologic response rate was evaluated in 103 patients and was observed to be superior in patients receiving the PCF regimen ($P < .036$). In the multivariate analyses of CR, the PCF schedule was the most important prognostic factor (odds ratio = 2.47; $P < .001$), together with disease stage and ECOG PS. This difference in response to induction chemotherapy resulted in a selection of more patients in the PCF arm for subsequent treatment with CRT established in the original protocol. The improved TTF

observed in favor of the PCF regimen could be explained by this selection because the relapse rate was similar in the two treatment arms (35% in CF arm and 38% in PCF arm).

Organ preservation was pursued in patients with laryngeal cancer and in patients with other primary tumors with initial resectable disease. This secondary objective was evaluated, and in this group of 134 patients, organ preservation was excellent (52% in CF group and 63% in PCF group, $P < .049$). It is important to note that our resectable patient population had poor prognostic factors, with only 30% of patients having stage III disease and 40% of the patients having tumors other than laryngeal cancers. Despite these observations, the median OS in patients with resectable disease has not yet been reached in both arms, with a mean survival, to date, of approximately 40 months (95% CI, 36 to 44 months). This survival figure is similar to the figures from other reports that included only laryngeal tumors and where more than 60% of the patients had stage III disease.[16] In this study, 84% of the patients had stage IV disease, 65% had unresectable tumors, and the majority of the patients (86%) did not have laryngeal primary tumors.

It is important to highlight that the percentage of events in the OS analysis after 24 months of median follow-up was 57% in the CF group *v* 46% in the PCF group ($P = .004$). Therefore, treatment with PCF reduced the number of events by 11%. In the Cox model for OS, disease stage, ECOG PS, resectability, and PCF regimen were the predictive variables of survival.

In summary, our findings indicate that induction chemotherapy with PCF is superior to CF in terms of CR rate. Additional follow-up is needed to obtain mature survival data. On the basis of these results, the PCF regimen should be the induction regimen selected for comparison of induction chemotherapy followed by CRT versus CRT alone. A phase II to III trial of induction chemotherapy with a taxane-based chemotherapy regimen plus CRT compared with CRT alone in patients with locally advanced HNC is currently underway.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ERRATA

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In Figure 3, Part C, the *P* value was given as ".614," whereas it should have been ".0614."

DOI: 10.1200/JCO.2006.01.901

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In Figure 1, the legend was given as, "Distribution of extra routine adverse event (RAE) data for unrelated and unlikely to be related RAEs (n = 10,247)," whereas it should have read, "Distribution of routine adverse event (RAE) data (n = 75,598)."

In Figure 2, the legend was given as, "Distribution of extra routine adverse event (RAE) data, by grade and attribution (n = 10,247)," whereas it should have read, "Distribution of extra routine adverse event (RAE) data for unrelated and unlikely to be related RAEs (n = 10,247)."

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