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Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial

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ABSTRACT

Purpose
Both concurrent chemoradiotherapy (CT-RT) and cetuximab radiotherapy (cetux-RT) have been established as the standard of care for the treatment of locally advanced squamous cell carcinoma of the head and neck. It was not known whether the addition of induction chemotherapy before cetux-RT could improve outcomes compared with standard of care CT-RT.

Patients and Methods
The current trial was restricted to patients with nonmetastatic N2b, N2c, or N3 squamous cell carcinoma of the head and neck and fit for taxotere, cisplatin, fluorouracil (TPF). Patients were randomly assigned to receive three cycles of TPF followed by cetux-RT versus concurrent carboplatin fluorouracil and RT as recommended in National Comprehensive Cancer Network guidelines. The trial was powered to detect a hazard ratio (HR) of 0.66 in favor of TPF plus cetux-RT for progression-free survival at 2 years. The inclusion of 180 patients per arm was needed to achieve 80% power at a two-sided significance level of .05.

Results
Between 2009 and 2013, 370 patients were included. All patients and tumors characteristics were well balanced between arms. There were more cases of grade 3 and 4 neutropenia in the induction arm, and the induction TPF was associated with 6.6% treatment-related deaths. With a median follow-up of 2.8 years, 2-year progression-free survival was not different between both arms (CT-RT, 0.38 *v* TPF + cetux-RT, 0.36; HR, 0.93 [95% CI, 0.73 to 1.20]; $P = .58$). HR was 0.98 (95% CI, 0.74 to 1.3; $P = .90$) for locoregional control and 1.12 (95% CI, 0.86 to 1.46; $P = .39$) for overall survival. These effects were observed regardless of p16 status. The rate of distant metastases was lower in the TPF arm (HR, 0.54 [95% CI, 0.30 to 0.99]; $P = .05$).

Conclusion
Induction TPF followed by cetux-RT did not improve outcomes compared with CT-RT in a population of patients with advanced cervical lymphadenopathy.

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INTRODUCTION

Head and neck cancers are common cancers—predominately squamous cell carcinomas (SCCHNs) of the oral cavity, larynx, oropharynx, and/or hypopharynx—and related to the use of alcohol and tobacco[1,2] A growing proportion of SCCs from the oropharynx are associated with human papillomavirus (HPV) in parallel with decreased tobacco consumption. HPV-positive cancers are generally associated with better outcomes compared with HPV-negative tumors, but there are important geographical variations in HPV-related oropharyngeal cancers.[3] The majority of patients with SCCHN present with locally and/or regionally advanced disease, with locoregional or distant failure rates between 30% and

ASSOCIATED CONTENT

Appendix
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Data Supplement
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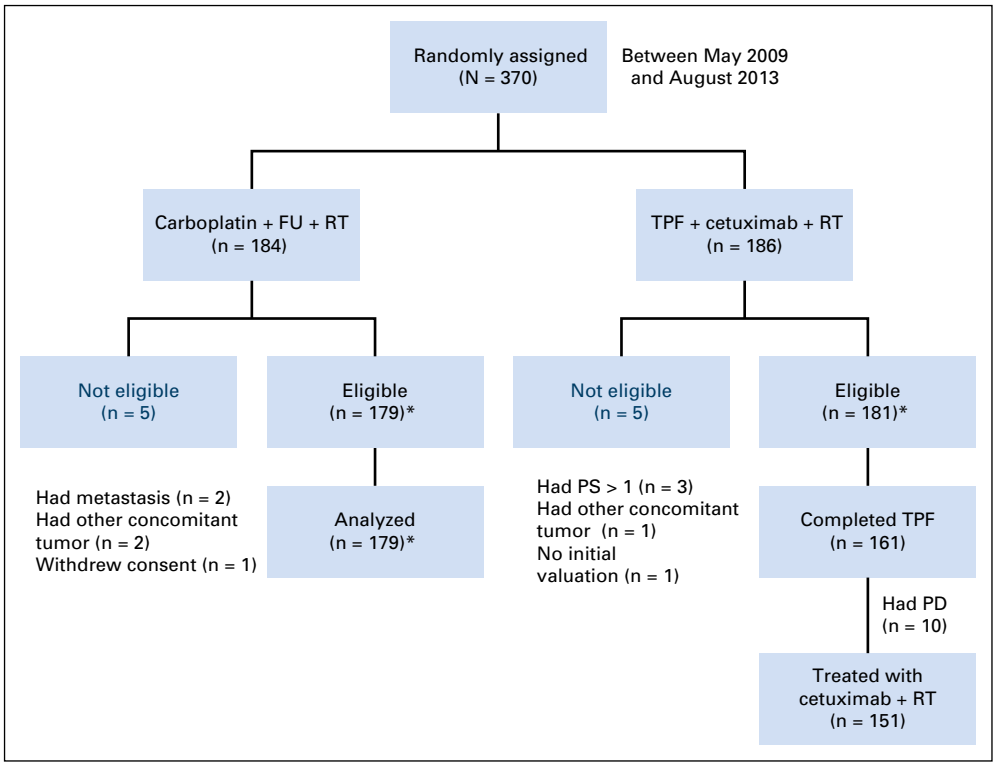

Fig 1. CONSERT diagram. Three hundred seventy patients were randomly assigned, 360 patients were eligible and analyzed, and five patients were ineligible in each arm. (*) Analysis performed on eligible patients: total n = 360. FU, fluorouracil; PD, progressive disease; PS, performance status; RT, radiotherapy; TPF, taxotere, cisplatin, fluorouracil.

65%.[4] On the basis of phase III randomized trials, concurrent chemoradiotherapy (CT-RT) is a well-established standard of care (SOC) for patients with nonoperated locally advanced SCCHN (LA-SCCHN).[5-7] The 5-year survival benefit of adding CT to radiotherapy (RT) compared with RT alone in the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) group was 6.5% and 13% for locoregional control.[7] The most common standard CT-RT regimen is a combination of conventional fractionated RT (70 Gy for 7 weeks) plus concomitant high-dose cisplatin (100 mg/m^2 every 3 weeks), as recommended in National Comprehensive Cancer Network (NCCN) guidelines.[6] An alternative CT-RT regimen also recommended as category 1 is the combination of conventional RT with carboplatin and fluorouracil (FU), which was used as the reference treatment in our study.[5,6] Finally, the combination of cetuximab, a monoclonal antibody that targets epidermal growth factor receptor, with RT has been established as an alternative SOC as recommended in NCCN guidelines.[6,8] Several attempts to challenge concurrent CT-RT either by adding induction chemotherapy, intensifying RT, and/or using alternative concurrent treatments failed to demonstrate a benefit compared with CT-RT alone[9-12]; however, induction TPF (docetaxel, FU, and cisplatin) could be of interest for decreasing the rate of distant metastases in patients with advanced nodal spread. Indeed, this was suggested by the DeCIDE trial,[11] which was restricted to patients with N2/N3 disease and showed a significant benefit of induction TPF in decreasing distant metastases.[11] This benefit in distant metastases, specifically for patients with N2/N3 disease, was also reported later in the update of the MACH-NC database when comparing induction TPF with FU and cisplatin.[13] This update of the MACH-NC database was based on six randomized trials and demonstrated the superiority of induction TPF compared with FU and cisplatin for overall survival (OS), progression-free survival (PFS), distant metastases, and locoregional control, thereby establishing the TPF regimen as a reference induction chemotherapy regimen in LA-SCCHN. The TPF regimen has also been established as a reference treatment in a larynx preservation strategy,[14] and in this context found to be feasible when followed by cetux-RT. In a recent randomized trial, TPF followed by cetux-RT demonstrated equivalent survival and a better toxicity profile compared with TPF followed by CT-RT.[15] On the basis of this rationale, whether TPF followed by cetux-RT could improve outcomes in patients with LA-SCCHN compared with CT-RT, which is the most well-established SOC, was an open question, and we tested this hypothesis in our study. Given the potential benefit of induction TPF on distant metastases, this study was restricted to a population of patients with bulky N2b-N3 disease that was known to be associated with a higher rate of distant metastases related to their massive nodal spread.

PATIENTS AND METHODS

Study Design and Patients

This study was a multicenter, randomized phase III trial. All patients gave written informed consent, and the study was performed in accordance with good clinical practice guidelines, the Declaration of Helsinki, and was approved by our local ethical committee (Nancy, Comité de Protection des Personnes de France-Est France). The current trial (GORTEC 2007-02) was restricted to patients with bulky nodal spread—N2b or N2c to N3—and was run in parallel with another complementary randomized trial (GORTEC 2007-01) that investigated the addition of concurrent chemotherapy to cetux-RT in patients with limited nodal spread, mainly N0 to N2a/N2b non–clinically palpable disease.

Between May 2009 and August 2013, 360 of 370 randomly assigned patients were eligible for treatment, with 181 in the TPF plus cetux-RT arm and 179 in the CT-RT arm. Ten patients were ineligible, five in each arm as shown in Figure 1. Inclusion criteria were as follows: age between 18 and 80 years, Eastern Cooperative Oncology Group performance status of 0 to 1, nonmetastatic, nonoperated stage III to IV histologically proven SCC of the oral cavity, oro/hypopharynx, and larynx, with N2b, N2c, or N3 nodal spread. HPV status was determined centrally for oropharyngeal cancer (OPC) using p16 immunostaining as a surrogate. p16 was considered positive when diffuse, strong, and homogeneous nuclear and cytoplasmic staining was $\geq$ 70% of tumor cells.

Patients must have had adequate liver, renal (creatinine clearance $\geq$ 60 ml/min), cardiac, and coronary function, and adequate hematologic blood counts to allow the delivery of TPF or carboplatin and FU.

Treatments

In the experimental arm, the TPF regimen was delivered as previously reported,[16,17] with docetaxel 75 mg/m^2 day 1 (T) plus cisplatin 75 mg/m^2 day 1 (P) plus FU 750 mg/m^2 days 1 to 5 (F), associated with the recommended use of prophylactic granulocyte colony-stimulating factor and the systematic use of ciprofloxacin from days 6 to 15 after chemotherapy. An evaluation was planned after three cycles, head and neck computed tomography or magnetic resonance imaging, and head and neck clinical evaluation. For all patients who achieved complete response (CR), partial response (PR), or stable disease, TPF was followed by cetux-RT administered as a loading dose of 400 mg/m^2 8 days before RT starting and a weekly dose of 250 mg/m^2 during RT for seven doses. Patients who experienced tumor and/or nodal progression after TPF were treated at the discretion of the investigators with either curative RT, palliative RT, or best supportive care. In the reference arm, RT was administered concurrently with chemotherapy, which consisted in three cycles of carboplatin 70 mg/m^2 per day plus FU 600 mg/m^2 per day for days 1 to 5 in continuous infusion, as previously reported.[9] In both arms, RT total dose was 70 Gy with 2 Gy per day, 5 days per week. Intensity-modulated RT was recommended, but three-dimensional conformal RT was also accepted. A dose of 50 Gy (2 Gy per day, 5 days per week) was prescribed to the prophylactic volume.

Random Assignment and Statistical Analysis

Random assignment between TPF plus cetux-RT and CT-RT was stratified by centers. To avoid deterministic minimization and assure allocation concealment, the treatment that minimized the imbalance was assigned with a probability of 0.80 (ie, $<$ 1.0). Random assignment was performed centrally at the GORTEC data center.

The primary end point was PFS, which was defined as the time from random assignment to first progression—locoregional or distant—or death from any cause. To detect a hazard ratio (HR) of 0.66 (increase in 2-year PFS from 45% to 59%), the inclusion of 180 eligible patients per arm was required to achieve 80% power at a two-sided significance level of .05. PFS analysis was performed according to the intent-to-treat principle on eligible patients and using a Cox proportional hazards regression model adjusted for the minimization factors. Secondary end points were OS, locoregional failure, distant failure, and acute or late toxicities according to NCI-CTCAE version 3 criteria. Median follow-up was estimated using the reverse Kaplan-Meier method.

RESULTS

Patient and Tumor Characteristics

All patients had biopsy-proven SCC of the oral cavity, oro/hypopharynx, or larynx. The distribution of patients according to age, performance status, tumor site, p16 immunostaining, and nodal and tumor stage were well balanced between the two arms and is given in Table 1. In both arms, the majority of patients had T3 to T4 and/or N2c to N3 disease. The inclusion of patients with N2b disease was allowed only if the cervical masses were clinically considered to be bulky (palpable). All patients with oral cavity carcinoma had unresectable disease in the neck and/or at the primary site. More than 60% of patients in both arms had an oropharyngeal cancer, with a majority being p16 negative (Tables 1 and 2). Figure 1 shows that five patients in both arms were not eligible—two distant metastasis, two patients with other concomitant tumor, and one patient withdrew consent in the CT-RT arm; and three patients with performance status of 2, one patient with other concomitant tumor, and one patient with no initial evaluation in the TPF plus cetux-RT arm—and random assignment was continued after including 360 patients, with 10 additional patients enrolled for a total of 370 patients, to maintain the initial plan of analyzing 360 patients.

Table 1. Patient and Tumor Characteristics

Characteristic	CT-RT (n = 179)	TPF + Cetux-RT (n = 181)
Male sex	153 (85)	157 (87)
Median age, years	56.5	56
Performance status		
0	63 (35)	71 (39)
1	116 (65)	110 (61)
Stage		
T2	29 (16)	30 (17)
T3	64 (36)	59 (33)
T4	86 (48)	91 (50)
Nodal status		
N2b	57 (32)	46 (26)
N2c	81 (45)	98 (54)
N3	41 (23)	37 (21)
Anatomic site		
Oral cavity	24 (14)	18 (10)
Oropharynx	108 (60)	123 (68)
Larynx	8 (5)	12 (7)
Hypopharynx	39 (22)	28 (15)

NOTE. Data are given as No. (%).
Abbreviations: cetux-RT, cetuximab radiotherapy; CT-RT, chemoradiotherapy; TPF, taxotere, cisplatin, fluorouracil.

Compliance With Treatment

In the experimental TPF plus cetux-RT arm (n = 181 patients), 1.5%, 10.5%, 5%, and 83% of the patients received zero or one, two, and three cycles of induction TPF, respectively. The proportion of the theoretical TPF dose administered was 99.1%, 97.3%, and 96.8% for cycles 1, 2, and 3 respectively. A total of 151 patients completed cetux-RT and 71% received at least seven injections of cetuximab.

In the reference CT-RT arm (n = 179 patients), 8.4%, 21.7%, and 69.5% of patients received zero or one, two, and three cycles, respectively, of concurrent carboplatin and FU during the course of RT. The proportion of the theoretical CT-RT dose administered was 97.9%, 99.1%, and 98.6% for cycles 1, 2, and 3, respectively.

Compliance with RT was not different between the two arms, with a mean overall treatment time of 52.3 days and 52.6 days in the TPF plus cetux-RT and CT-RT arms, respectively. Mean radiation dose was 68.2 Gy (standard deviation, 7.7) in 175 patients in the CT-RT arm and 69.2 Gy (standard deviation, 5.9) in 151 patients in the TPF plus cetux-RT arm who received RT. The

Table 2. p16 Status in Patients With Oropharyngeal Tumors (172 analyzed and 59 unknown)

p16 Status	CT-RT (n = 84), No. (%)	TPF + Cetux-RT (n = 88), No. (%)
Negative	58 (69)	69 (78)
Positive	26 (31)	19 (21)

proportion of temporary RT interruption (≥ 7 days) was 18% and 13%, and discontinuation of RT was 3% and 8% in the TPF plus cetux-RT and CT-RT arms, respectively.

To evaluate a potential imbalance of RT quality between the two arms, a review of the quality assurance of RT was performed by GORTEC quality assurance experts. RT records of the first two patients of each center were analyzed, and one third of the other enrolled patients per center were also reviewed. Items reviewed included total dose, planned target volume of 70 Gy coverage, dose to spinal cord and brainstem, dose per fraction, overall treatment time, and adequate verification imaging. No difference in any of these items was observed between both arms.

Tolerance and Response to TPF in the Experimental Arm

Despite the recommended prophylactic use of lenograstim and the systematic use of ciprofloxacin, 30 patients had febrile neutropenia (17%) and 12 patients died during or in the 30 days after TPF (6.6%), and all causes of death, with the exception of one, were considered to be related to TPF. Among these 12 patients, three died at home of unknown cause and were registered as toxic deaths, one patient died of hemorrhage (registered as toxic death), six patients died from infectious disease with neutropenia (five grade IV and one grade III), and two patients died as a result of diarrhea and renal failure (one patient was reclassified as septic shock). Overall, the most common pattern of death was infectious disease, mainly associated with neutropenia. Of 181 patients who received TPF, seven patients (4%), 73 (40.5%), 71 (39%), and 10 (5.5%) exhibited CR, PR, disease stabilization, or disease progression, respectively, after induction TPF. After TPF, 20 patients did not complete the evaluation and did not receive RT as initially planned, and 10 additional patients who experienced progression with TPF did not receive RT. Overall, only 151 (83%) of 181 patients were treated with cetux-RT as planned.

Adverse Events

The rate of grade 3 and 4 adverse events is listed in Table 3. We observed significantly more grade 3 and 4 fever (6% *v* 0.6%; $P < .001$), grade 3 and 4 neutropenia (26% *v* 6%; $P < .001$), and significantly more febrile neutropenia (17% *v* 0%; $P < .001$) in the TPF plus cetux-RT arm. Grade 3 and 4 mucositis was not different between the two arms—50% in the CT-RT arm versus 48% in the cetux-RT arm ($P = .7$). Grade 3 and 4 skin reactions inside RT fields were significantly increased in the cetux-RT arm compared with the CT-RT arm (53% *v* 29%, respectively; $P < .001$). In contrast to 6.6% TPF-related deaths, only one patient died during CT-RT (0.6%; $P = .0016$). There was also a difference between the two arms for grade 3 and 4 skin reactions outside RT fields, with 11% in the cetux-RT arm and 7% grade 3 and 4 hypersensitivity to cetuximab. Other relevant toxicities were not different between the two arms.

Oncologic Results

Median follow-up was 2.8 years for the TPF plus cetux-RT arm (interquartile range, 1.9 to 4.0) and 2.6 years for the CT-RT arm (interquartile range, 2.2 to 3.8). There was no difference in PFS between the two arms with an HR of 0.93 (95% CI, 0.73 to 1.20; $P = .58$), no difference for locoregional control with an HR of 0.98 (95% CI, 074 to 1.30; $P = .90$; Figs 2A and 2B), and finally no difference in OS with an HR of 1.12 (95% CI, 0.86 to 1.46; $P = .39$; Fig 2C). A significant difference was observed in favor of the TPF plus cetux-RT arm regarding the rate of distant metastases when considered as a first event with an HR of 0.54 (95% CI, 0.30 to 0.99; $P = .05$; Fig 2D) and also when considered as the first or later event with an HR of 0.62 (95% CI, 0.40 to 0.95; $P = .03$; Appendix Fig A1, online only).

Oncologic Results by p16 Status

p16 expression was assessed by immunostaining in 172 patients with OPC (74%) with 84 in the CT-RT arm and 88 in the TPF

Table 3. Occurrence of Grade 3 and 4 Adverse Events

	RT-CT (%)		TPF (%)		Cetux-RT (%)		
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	*P*
Fever	0.6	—	9.0	—	2.0	—	.001
Mucositis (RTOG)	48.0	2.0	3.0	—	46.0	2.0	
Neutropenia	3.0	3.0	8.0	18.0	—	—	.001
Renal toxicity	0.6	—	3.5	—	2.5	—	
Liver enzyme	4.0	—	—	—	1.0	—	
Skin reactions			NA	NA			.001
Outside RT fields	—	—			10.0	1.0	
Inside RT fields	28.0	1.0			48.0	5.0	
Hypersensitivity to cetuximab (n = 151)	NA	NA	NA	NA	5.0	2.0	

NOTE. There was significantly more grade 3 and 4 fever (9% with TPF *v* 0.6%; $P = .001$), grade 3 and 4 neutropenia (26% *v* 6%; $P < .001$), and significantly more febrile neutropenia (17% *v* 0%; $P < .001$) in the TPF+ cetux-RT arm. Grade 3 and 4 mucositis was not different between the two arms: 50% in the CT-RT arm *v* 48% in the cetux-RT arm ($P = .7$). Grade 3 and 4 skin reactions inside radiotherapy fields were significantly increased during cetux-RT compared with CT-RT (53% *v* 29%, respectively; $P < .001$).

Abbreviations: cetux-RT, cetuximab radiotherapy; CT-RT, chemoradiotherapy; NA, not applicable; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; TPF, taxotere, cisplatin, fluorouracil.

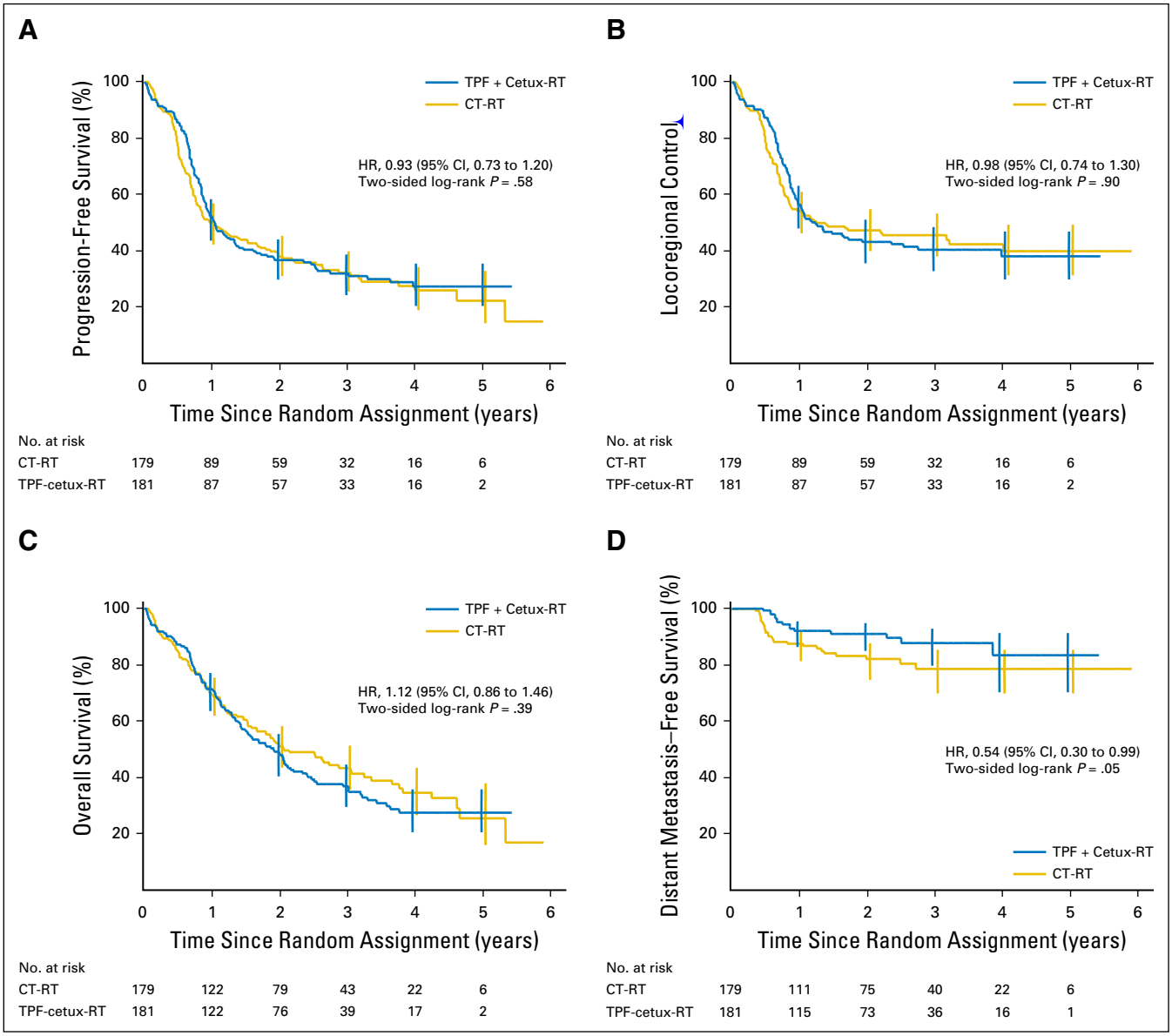

Fig 2. (A) Progression-free survival. (B) Locoregional control. (C) Overall survival. (D) Distant metastasis–free survival (first event), showing a significant difference in favor of the taxotere, cisplatin, fluorouracil (TPF) plus cetuximab radiotherapy (cetux-RT) arm. CT-RT, chemoradiotherapy; HR, hazard ratio.

plus cetux-RT arm. Twenty-six patients were found to be p16 positive in the CT-RT arm (31%) and 19 in the TPF plus cetux-RT arm (21.5%). Only eight (18%) of 45 p16-positive patients were nonsmokers, which indicates that the majority of patients with OPC were p16 negative (74%) and smokers (90%). Overall, a significant improvement in PFS was found in p16-positive OPC compared with p16-negative OPC ($P < .001$); however, the absence of benefit for PFS associated with TPF plus cetux-RT compared with CT-RT was observed both in p16-positive OPC with an HR of 0.78 (95% CI, 0.28 to 2.20; $P = .64$) and in p16-negative OPC with an HR of 1.28 (95% CI, 0.84 to 1.93; $P = .25$), and the interaction between p16 and treatment modality was not significant ($P = .35$). Finally, the benefit in favor of TPF plus cetux-RT with regard to distant metastasis was not different between p16-positive and p16-negative OPC

DISCUSSION

Two phase III randomized trials were run in parallel within the GORTEC network. The current study was restricted to patients with stage IV bulky nodal, N2b clinically palpable, or N2c or N3 disease, whereas the second trial (GORTEC 2007-01) was restricted to patients with limited nodal disease and assessed the addition of concurrent chemotherapy to the cetux-RT SOC.

In the current study, in addition to the N2b to N3 status, a majority of patients were smokers (90%) with T4 and p16 negative disease, which indicated that nearly all fell into the high-risk category as described by Ang et al.[18] The effect of induction TPF followed by cetux-RT compared with well-established SOC CT-RT in this particular selection of patients was unknown. Our

study failed to find a benefit for PFS in favor of the TPF approach, and the primary end point was not met. Overall, relatively similar results were observed in PFS, locoregional control, and OS between the two arms. There was one interesting finding regarding the decrease in distant metastases—either as the first or nonfirst event—that was observed in the TPF arm, which confirmed the hypothesis that TPF can be active in micrometastases and could be of interest in patients with the most advanced nodal spread who carry the highest risk of distant metastases. This observation is in agreement with the DeCIDE[11] randomized trial, which was also restricted to patients with N2/N3 disease and demonstrated a comparable benefit of TPF on distant metastases. This observation is also in agreement with the update of the MACH-NC database when comparing induction TPF with induction FU and cisplatin.[13]

Overall, use of induction TPF markedly modified the clinical presentation of the disease as only 151 (83%) of 181 patients who were randomly assigned to TPF could be offered RT as planned (cetux-RT) after induction TPF, either because they died or because of disease progression or as a result of other interferences. This implies that 17% of patients in this arm did not have the opportunity to receive curative RT, which may have a substantial influence on final outcomes in patients compared with SOC CT-RT, in which the majority of patients received full-dose RT (92%). This observation is in good agreement with other randomized studies in locally advanced head and neck cancer, such as the Tremplin[15] study, in which a large proportion of patients (37 [24%] of 153) who received induction TPF could not receive additional RT as planned.

We report an 83% disease in control rate after induction TPF, but the objective response rate was only 45.5% (CR + PR), which is lower than the response rates of 60% or more that have been reported in other phase III studies by Vermorken et al[16] and Cohen et al.[11] This may be as result, in part, of our selection of patients, essentially with more advanced and bulky disease (N2c to N3; 75%). Another aspect related to TPF in our patients with classical tobacco- and alcohol-related SCCHN and mostly p16-negative disease was the high rate of TPF-related deaths (6.6%), which might not be acceptable. This rate was significantly higher than that observed in the CT-RT arm and in agreement with other randomized studies that investigated induction TPF. Indeed, in these studies, TPF-related death has been reported to be 0% (in a randomized study on nasopharynx),[19] and 2.9% in the DeCIDE[11] randomized trial and 5% in the seminal randomized trial reported by Vermorken et al.[16] These considerations do suggest that, if TPF is a reference induction chemotherapy regimen, which was found to be superior to cisplatin and FU, it should be carefully handled, especially in this type of patient with advanced local disease and tobacco- and alcohol-related comorbidities, as was the case with our study.

In conclusion, compared with the well-established CT-RT SOC, induction TPF followed by cetux-RT failed to provide a benefit in PFS, locoregional control, and OS in a selection of patients with N2b to N3 LA-SCCHN. A benefit from TPF on distant metastases confirmed previous observations, but this should be carefully considered, given the potential TPF-related toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial

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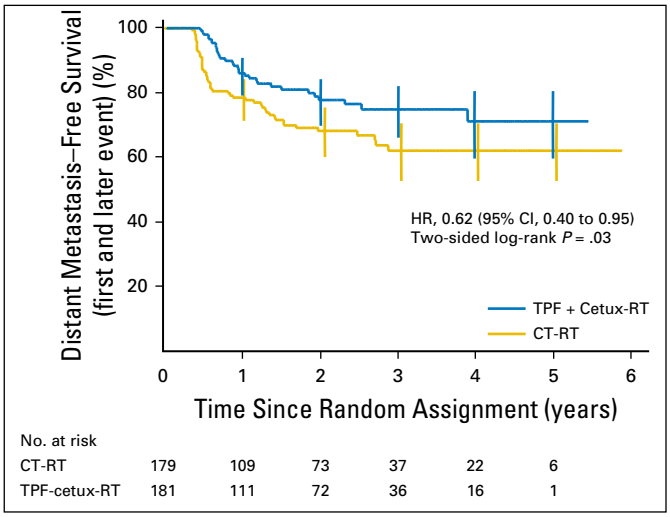

Fig A1. Distant metastasis–free survival (first and later event), with a significant difference in favor of the taxotere, cisplatin, fluorouracil (TPF) plus cetuximab radiotherapy (cetux-RT) arm. CT-RT, chemoradiotherapy; HR, hazard ratio.