

A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer

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Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for patients with unresectable, nonmetastatic locoregionally advanced squamous-cell carcinoma of the head and neck (LASCCHN). This randomized, open-label, phase III clinical trial compared the efficacy between standard CCRT and two different induction chemotherapy (ICT) regimens followed by CCRT.

Patients and methods: Patients with untreated LASCCHN were randomly assigned to ICT (three cycles), with either docetaxel (Taxotere), cisplatin and 5-fluorouracil (TPF arm) or cisplatin and 5-fluorouracil (PF arm), followed by CCRT [7 weeks of radiotherapy (RT) with cisplatin 100 mg/m² on days 1, 22 and 43]; or 7 weeks of CCRT alone. The primary end points were progression-free survival (PFS) and time-to-treatment failure (TTF).

Results: In the intention-to-treat (ITT) population ($n = 439$), the median PFS times were 14.6 (95% CI, 11.6–20.4), 14.3 (95% CI, 11.8–19.3) and 13.8 months (95% CI, 11.0–17.5) at TPF-CCRT, PF-CCRT and CCRT arms, respectively (log-rank $P = 0.56$). The median TTF were 7.9 (95% CI, 5.9–11.8), 7.9 (95% CI, 6.5–11.8) and 8.2 months (95% CI, 6.7–12.6) for TPF-CCRT, PF-CCRT and CCRT alone, respectively (log-rank $P = 0.90$). There were no statistically significant differences for overall survival (OS). Toxic effects from ICT-CCRT were manageable.

Conclusion: Overall, this trial failed to show any advantage of ICT-CCRT over CCRT alone in patients with unresectable LASCCHN (ClinicalTrials.gov number, NCT00261703).

Key words: chemoradiotherapy, head and neck cancer, induction chemotherapy, unresectable

introduction

Squamous-cell carcinoma of the head and neck (SCCHN) accounts for roughly 9% of cancers worldwide [1]. Most patients present with locoregionally advanced disease (LASCCHN) at diagnosis. In this stage, 40%–60% of patients relapse and 30%–50% of patients live for 3 years after treatment with surgery and radiotherapy (RT) [2, 3]. Randomized trials have investigated

the efficacy of chemotherapy (Ct) in LASCCHN [4, 5]. Ct has been used as induction treatment (ICT), concomitantly with RT (concurrent chemoradiotherapy, CCRT), or as adjuvant treatment after RT, surgery or both. CCRT improves survival over RT, generally attributed to improved locoregional control (LRC). However, little impact of CCRT on distant metastases has been observed [4].

ICT can reduce metastases incidence [6], and cisplatin-based ICT induces response rates of 80%–90%, with complete response (CR) rates of 20%–40%, in LASCCHN [7].

This trial assessed if ICT followed by CCRT is superior to CCRT alone, and which ICT regimen is more active in unresectable LASCCHN.

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patients and methods

This study was a phase III, open-label, three-arm, randomized, multicenter, clinical trial. It was approved by the Local Research Ethics Committees and was executed in accordance with the Declaration of Helsinki, Good Clinical Practice, and local ethical and legal requirements. All patients, enrolled from 19 Spanish centers signed informed consent.

eligibility criteria

The study included patients (≥ 18 years) with histologically confirmed LASCCHN (stage III/IV; according to the fifth edition of the American Joint Committee on Cancer), non-metastatic, unresectable, without previous Ct, RT and surgery. The definition of unresectable disease was based on the clinical exploration and magnetic resonance imaging (MRI) or computed tomography (CT) imaging, according to the Northern California Oncology Group [8]. Additional eligibility criteria included oral cavity, oropharynx, hypopharynx or larynx as primary tumor sites; ≥ 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) Criteria v1.0 [9], Eastern Cooperative Oncology Group (ECOG) 0–1 and adequate hematologic, hepatic and renal functions, including neutrophils $\geq 2000/\text{mm}^3$, platelets $\geq 100\,000/\text{mm}^3$, hemoglobin ≥ 10 g/dl, bilirubin $\leq 1 \times$ upper limit of normal (ULN), ALT $\leq 2.5 \times$ ULN, AST $\leq 2.5 \times$ ULN, alkaline phosphatase $\leq 5 \times$ ULN. Patients with both alkaline phosphatase $> 2.5 \times$ ULN and AST and/or ALT $> 1.5 \times$ ULN were not eligible. Patients should have serum creatinine ≤ 1.4 mg/dl, and for those with serum creatinine > 1.4 mg/dl, a creatinine clearance > 60 ml/min, calculated by the Cockcroft and Gault equation, was required. Patients with grade ≥ 2 peripheral neuropathy were not eligible. In accordance with the protocol, most of the evaluations were conducted within 7 days of randomization, while some of them were carried out within 21 days of randomization; and included a complete medical history, physical examination, hematologic and biochemical analyses, electrocardiography, endoscopy, MRI or CT of the head and neck, and chest radiography with or without CT.

study design

The primary objective was to compare the efficacy of three different treatment programs with respect to progression-free survival (PFS) and time-to-treatment failure (TTF). Randomization to one of the three treatment arms was central and stratified according to the primary tumor site. Once the planned 128 patients at the CCRT-alone arm were recruited, the patients were only randomly assigned to TPF-CCRT and PF-CCRT arms (see below). ICT arms (three cycles of 21 days each, q3w) included cisplatin (day 1) and 5-fluorouracil (days 1–5; cIV) with or without docetaxel (day 1) (Taxotere, Sanofi-Aventis Spain) 75 mg/m² (TPF and PF arms), followed by 7 weeks of CCRT. ICT doses of cisplatin and 5-fluorouracil were 75 mg/m² and 750 mg/m²/day (TPF), and 100 mg/m² and 1000 mg/m²/day (PF), respectively. The non-ICT arm consisted of 7 weeks of CCRT. CCRT consisted of a standard RTOG regimen with cisplatin 100 mg/m² (days 1, 22 and 43) plus RT (conventional fractionation in a 1.8–2.0 Gy once daily fraction, 5 days a week until the total tumor dose of 70 Gy) and 50 Gy in the lymph node area in case of microscopic disease). CCRT started 3–8 weeks after the end of the third TPF and PF cycles.

G-CSF administration from the first cycle, to patients assigned to TPF, was implemented in the protocol, by amendment, to prevent neutropenia, in May 2006. Prophylactic ciprofloxacin (500 mg po bid) was given to the TPF group, from the first cycle, from days 6–12 of each cycle. Neck or primary residual tumor resections after CCRT were elective, after assessment by a multidisciplinary team, and allowed by the protocol.

This trial was designed as a phase II/III trial, in which the results of the phase II part (response assessment in 200 patients) were to define the two arms in the phase III part. Data on a different response with TPF versus PF

were not known in 2002. However, the phase III part continued with three arms, because the difference in objective response rates (ORR) proved to be not significantly different at the end of the phase II part.

assessments

Objective response and adverse events were assessed through the RECIST criteria, and the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) v2.0, respectively.

Tumor clinical assessment was carried out every 3 weeks during the treatment period. Head and neck imaging (CT/MRI) was carried out at the end of both ICT and CCRT periods, and in case of disease progression. Toxicity was weekly evaluated through clinical assessments, including hematological tests.

sample size

The following assumptions were made for the phase III sample size: an increase in median TTF from 8 to 12 months (HR, 0.67) between ICT-CCRT and CCRT, and from 10 to 15 months between TPF-CCRT versus PF-CCRT; with a 15% PFS difference at 2 years between ICT-CCRT versus CCRT and TPF-CCRT versus PF-CCRT. Considering a 25% of loss rate for ICT-CCRT and 10% for CCRT, $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power = 80%); the number of patients needed to meet both assumptions, according to the log-rank test, were 155 and 128 for ICT-CCRT and CCRT arms, respectively.

statistical analysis

Efficacy analyses were carried out in both intention-to-treat (ITT) and per protocol (PP) populations. The ITT population consisted of all randomized patients. The PP population was formed, in both ICT-CCRT arms, by all randomized patients who had received at least one ICT cycle and another one of CCRT. Patients assigned to CCRT alone who received one or more cycle of CCRT were included in the PP population. All early progressions and tumor-related deaths were included in this population.

The primary end points were the comparison of PFS and TTF of the three treatment arms in both the ITT and the PP populations. PFS was defined as the time from randomization to either progression or death (regardless of the cause of death). TTP was defined as the time from randomization to progression, recurrence, death, withdrawal due to adverse event, patient refusal or loss of follow-up, any surgical intervention or any other antitumor treatment in those patients in whom CR was not obtained. Secondary end points included safety profile, overall survival (OS) and LRC in both the ITT and PP populations.

OS was calculated as the elapsed time from randomization until death, regardless of the cause. LRC was considered to be present when a patient showed CR since randomization, either during the treatment or thereafter, with no salvage surgery.

PFS, OS and TTF analyses were carried out according to the Kaplan-Meier method with log-rank testing to assess differences between groups. Multivariate analysis was carried out using the Cox proportional hazards regression model to estimate adjusted hazard ratios. Categorical and continuous variables were compared through the Fisher's exact test and the Wilcoxon test, respectively.

All tests were two-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were carried out by using SAS (SAS Institute, Cary, NC).

results

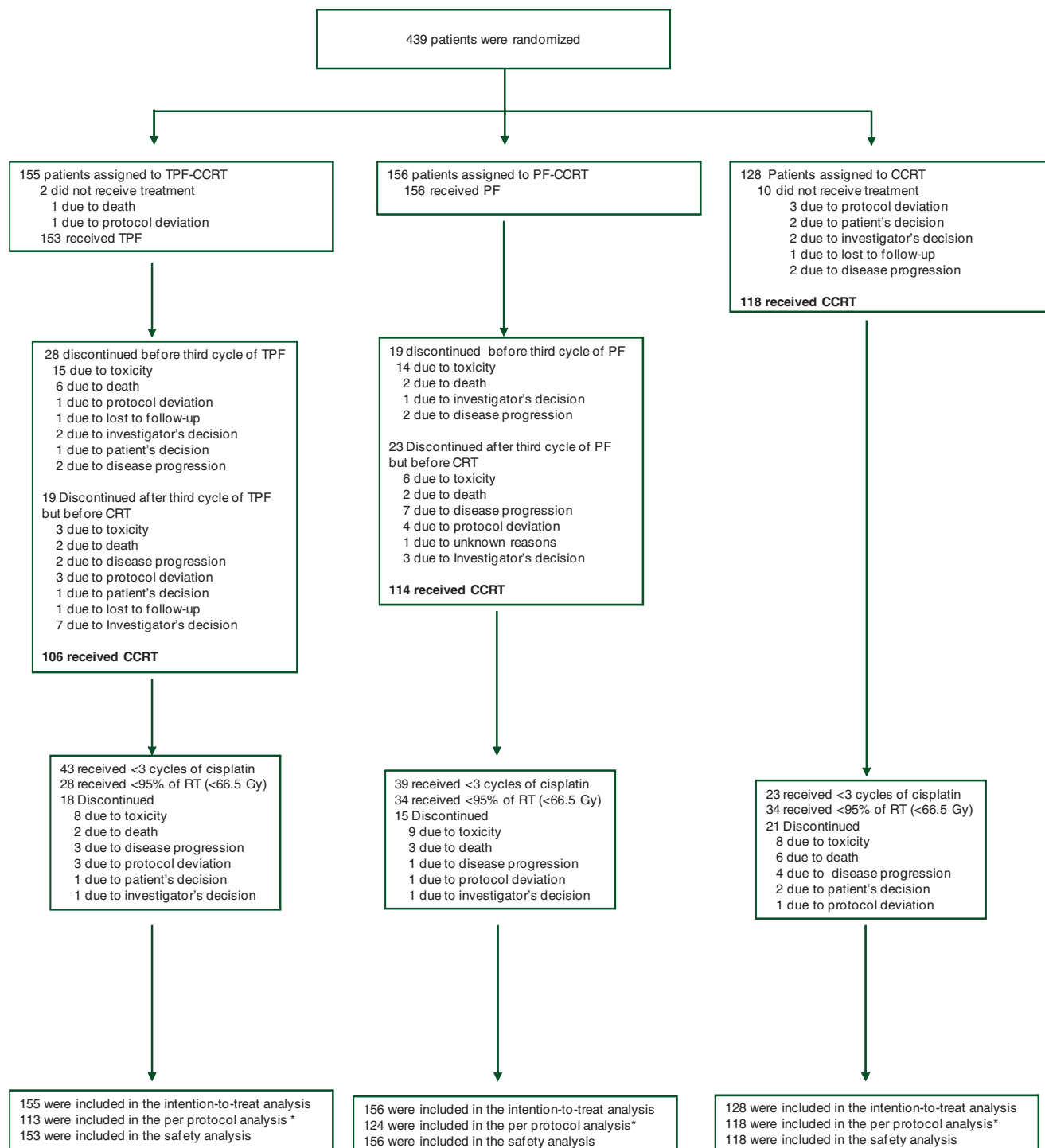
patients

Between December 2002 and May 2007, 439 patients were randomly assigned: 155 to TPF-CCRT, 156 to PF-CCRT and 128 to

CCRT alone (ITT population, Figure 1). Treatment groups were generally well balanced (Table 1). Most patients had ECOG performance status 1, most primary tumors were stage IV (>95%), were of grade 2 histology and located in the oropharynx in over 40% in each arm of the study.

treatment

The median time elapsed between randomization and the start of treatment was 5, 4 and 17 days in the TPF arm, PF arm and the CCRT alone arm, respectively. A substantial number of patients did not start treatment (10 in CCRT alone,



*In the per protocol population: 78 out of 113 patients completed RT at TPF-CCRT arm, 80 out of 124 patients at PF-CCRT arm and 84 out of 118 patients CCRT alone arm

Figure 1. Flow of trial participants.

2 TPF-CCRT), or did not receive CCRT after induction (47 after TPF, 42 after PF). Nineteen patients in the TPF arm and 23 in the PF arm completed ICT, but did not receive CCRT. Of those who started CCRT in the three arms, this was discontinued in

18, 15 and 21 patients in the TPF, PF and CCRT alone arm, respectively. Forty-seven, 39 and 23 of those who started CCRT in the TPF, PF and CCRT alone arm, respectively, received less than the planned 3 cisplatin cycles and 28, 34, and 34 in the

Table 1. Baseline patient and tumor characteristics

Patient characteristics	TPF*-CCRT (n = 155)	PF*-CCRT (n = 156)	CCRT (n = 128)	P value
Age (years)				0.58
Median	58.1	57.5	56.5	
Range (min-max)	35.7-78.8	35.1-85.3	25.1-80.0	
Sex, n (%)				0.48
Male	145 (93.6)	145 (93.0)	115 (89.8)	
Female	10 (6.5)	11 (7.1)	13 (10.2)	
ECOG, n (%) ^a				0.58
0	45 (29.0)	48 (30.8)	33 (25.8)	
1	108 (69.7)	103 (66.0)	94 (73.4)	
Primary disease site, n (%)				1.00
Oropharynx	66 (42.6)	67 (43.0)	54 (42.2)	
Oral cavity	33 (21.3)	34 (21.8)	26 (20.3)	
Larynx	29 (18.7)	27 (17.3)	25 (19.5)	
Hypopharynx	27 (17.4)	28 (18.0)	23 (18.0)	
Tumor status, n (%)				0.84
T0	0 (0.0)	0 (0.0)	1 (0.8)	
T1	1 (0.7)	2 (1.3)	1 (0.8)	
T2	17 (11.0)	14 (9.0)	12 (9.4)	
T3	18 (11.6)	16 (10.3)	18 (14.1)	
T4	119 (76.8)	124 (79.5)	96 (75.0)	
Node status, n (%)				0.51
N0	27 (17.4)	27 (17.3)	19 (14.8)	
N1	25 (16.1)	24 (15.4)	29 (22.7)	
N2	90 (58.1)	85 (54.5)	64 (50.0)	
N3	13 (8.4)	20 (12.8)	16 (12.5)	
Tumor stage, n (%)				1.00
Any location, III	3 (1.9)	4 (2.6)	3 (2.3)	
Any location, IV	152 (98.1)	152 (97.4)	125 (97.7)	
Tumor stage, n (%)				1.00
Oropharynx, III	2 (3.0)	2 (3.0)	1 (1.9)	
Oropharynx, IV	64 (97.0)	65 (97.0)	53 (98.1)	
Tumor stage, n (%)				0.74
Oral cavity, III	0 (0.0)	1 (2.9)	1 (3.9)	
Oral cavity, IV	33 (100.0)	33 (97.1)	25 (96.2)	
Tumor stage, n (%)				NA
Larynx, III	0 (0.0)	0 (0.0)	0 (0.0)	
Larynx, IV	29 (100.0)	27 (100.0)	25 (100.0)	
Tumor stage, n (%)				1.00
Hypopharynx, III	1 (3.7)	1 (3.6)	1 (4.4)	
Hypopharynx, IV	26 (96.3)	27 (96.4)	22 (95.6)	
Histologic grade, n (%) ^b				0.29
G1	16 (15.4)	23 (22.8)	14 (15.9)	
G2	58 (55.8)	40 (39.6)	43 (48.9)	
G3	18 (17.3)	27 (26.7)	18 (20.5)	
G4	0 (0.0)	2 (19.8)	2 (2.3)	
GX	12 (11.5)	9 (8.9)	11 (12.5)	

*TPF denotes docetaxel plus cisplatin and 5-fluorouracil, and PF denotes cisplatin and 5-fluorouracil.

^aECOG status was unknown for 2, 5 and 1 patients from arms A, B and C, respectively.

^bHistologic grade was unknown for 51, 55 and 40 patients from arms A, B and C, respectively.

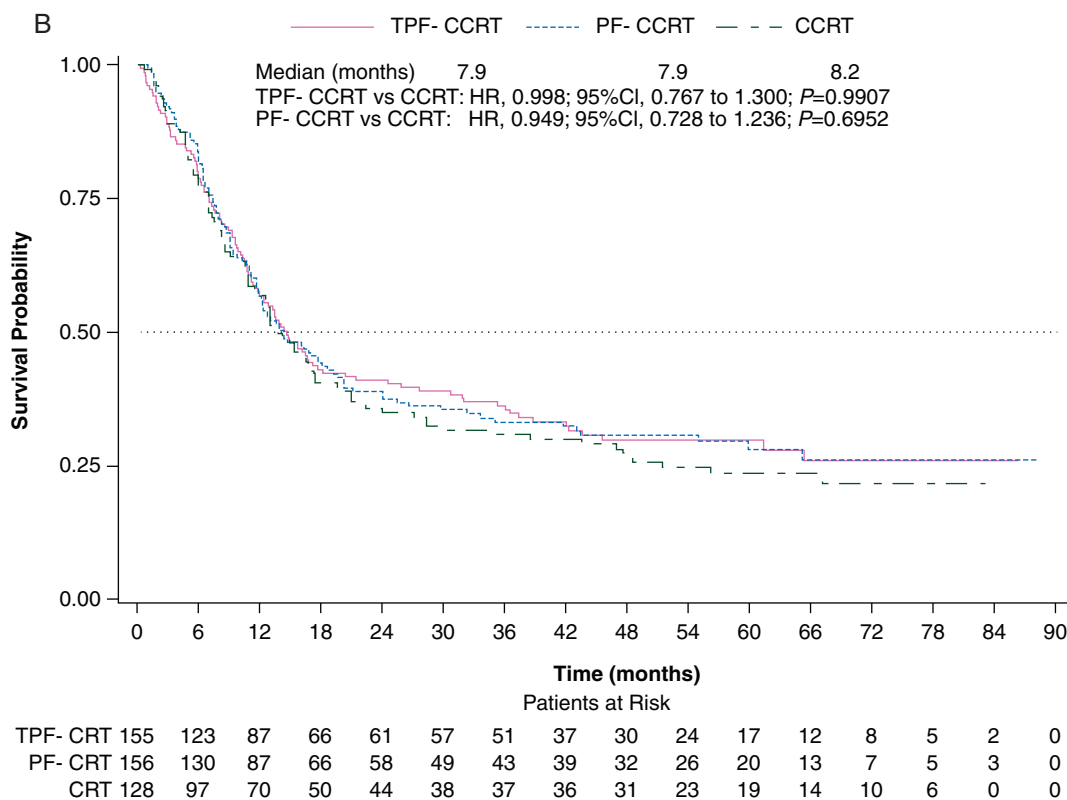
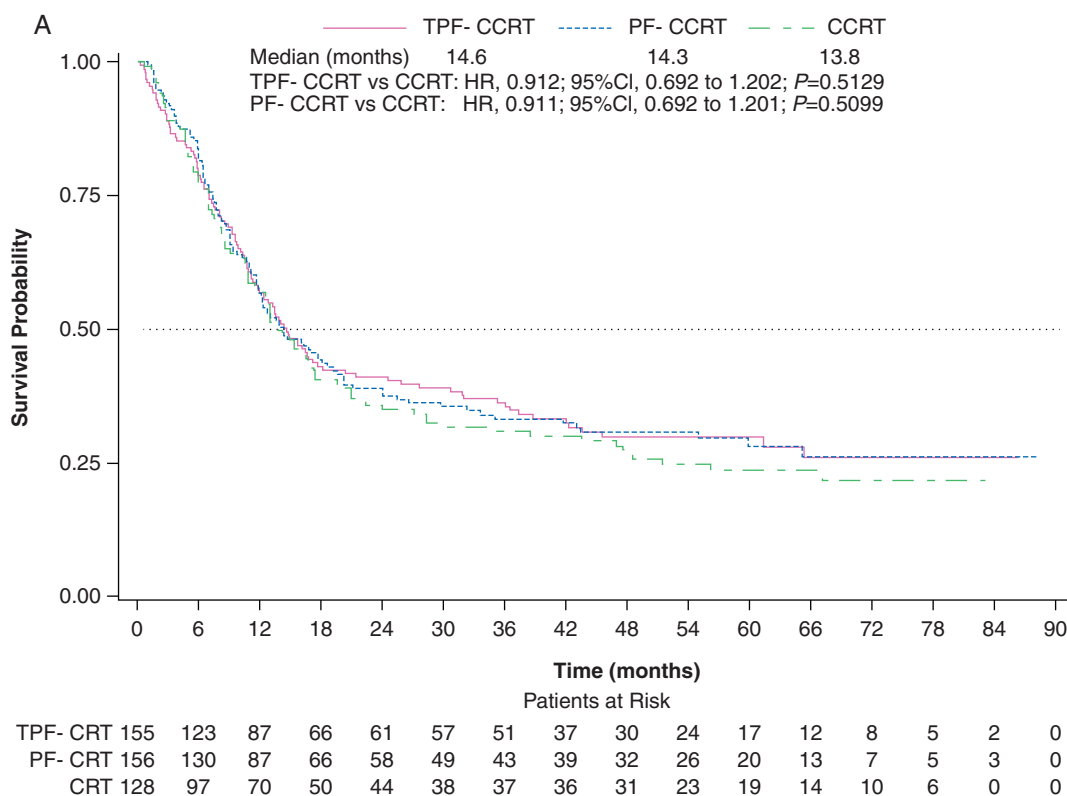


Figure 2. (A) Progression-free survival (PFS, ITT population). (B) Time-to-treatment failure (TTF, ITT population). (C) Overall survival (OS, ITT population).

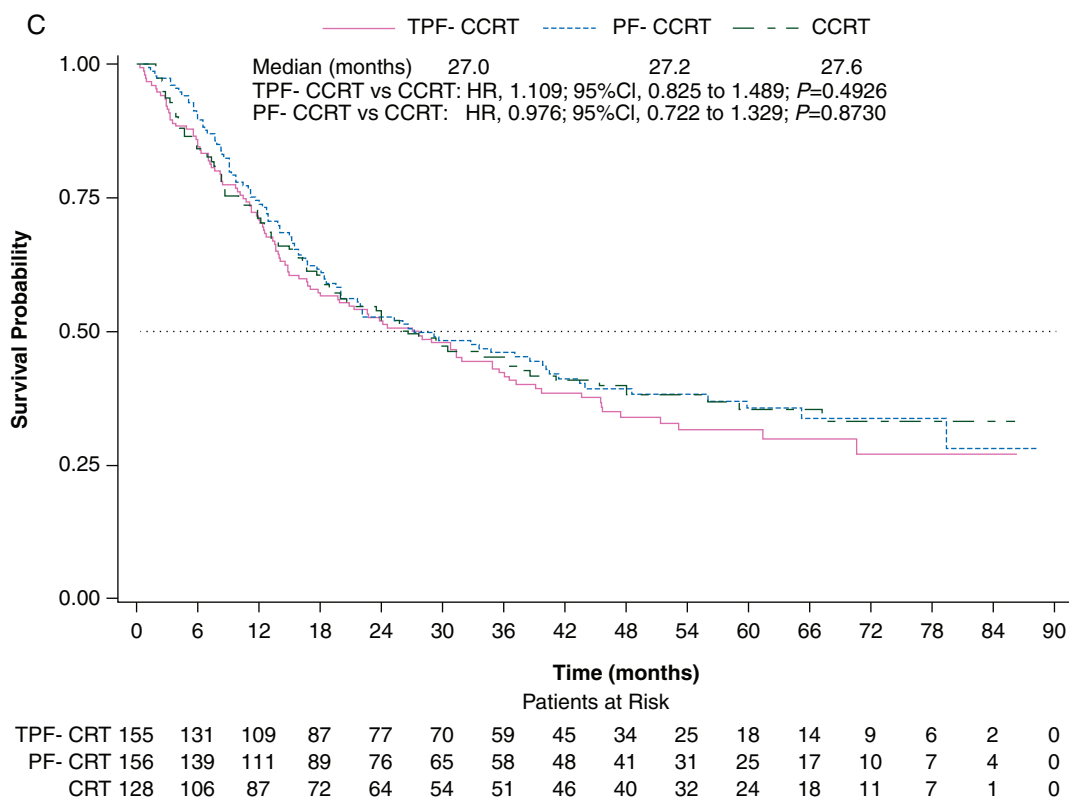


Fig. 2 Continued

three arms, respectively received less than 95% of the planned RT dose (Figure 1). The PP population consisted of 355 patients, 113 in the TPF-CCRT arm, 124 in the PF-CCRT arm and 118 in the CCRT alone arm. Forty-five patients showed >5% of weight loss during the study; 11 (7.1%), 15 (9.6%) and 19 (14.8%) patients from TPF-CCRT, PF-CCRT and CCRT arms, respectively.

efficacy

The median follow-up were 23.8 (range 0.4–86.3), 22.1 (range 1.2–88.2) and 23.7 months (range 0.5–86.1) for TPF-CCRT, PF-CCRT and CCRT groups, respectively, in the ITT population; and 31.4 months for TPF-CCRT (range 1.4–86.3), 26.4 months for PF-CCRT (range 1.6–88.2) and 24.9 months for CCRT (range 1.9–86.1), in the PP population.

In the ITT population, the median PFS were 14.6 (95% CI, 11.6–20.4), 14.3 (95% CI, 11.8–19.3) and 13.8 months (95% CI, 11.0–17.5) in the TPF-CCRT, PF-CCRT and CCRT arms, respectively (log-rank $P=0.56$). The comparisons TPF-CCRT versus CCRT (HR, 0.912; 95% CI, 0.692–1.202) and PF-CCRT versus CCRT did not show significant differences (HR, 0.911; 95% CI, 0.692–1.201) (Figure 2A). The median TTF were 7.9 (95% CI, 5.9–11.8), 7.9 (95% CI, 6.5–11.8) and 8.2 months (95% CI, 6.7–12.6) for TPF-CCRT, PF-CCRT and CCRT alone, respectively (log-rank $P=0.90$) (Figure 2B). The median OS were 27.0 (95% CI, 17.0–36.1), 27.2 (95% CI, 19.5–40.4) and 26.6 months (95% CI, 18.3–41.1) for TPF-CCRT, PF-CCRT and CCRT, respectively (n.s.) (Figure 2C).

In the PP population, the median PFS of the patients allocated to ICT-CCRT arms was higher than that of the CCRT arm. The median PFS for TPF-CCRT was 20.4 months (95% CI, 13.8–38.7), 18.1 months for PF-CCRT (95% CI, 12.4–26.6) and 13.3 months (95% CI, 10.9–17.9) for CCRT alone (log-rank $P=0.083$). The comparison of TPF-CCRT versus CCRT showed a significant benefit of TPF-CCRT for PFS (HR, 0.719; 95% CI, 0.526–0.983; $P=0.03$), but not the corresponding comparison between PF-CCRT and CCRT (HR, 0.774; 95% CI, 0.572–1.047; $P=0.09$) (Figure 3A). The median TTF were 14.0 (95% CI, 10.8–30.8), 12.4 (95% CI, 9.4–18.7) and 8.6 months (95% CI, 7.0–13.0) for TPF-CCRT, PF-CCRT and CCRT, respectively (log-rank $P=0.038$). The comparisons versus the CCRT arm showed significant benefits for ICT-CCRT arms (TPF-CCRT versus CCRT: HR, 0.700; 95% CI, 0.518–0.947; $P=0.0205$; PF-CCRT versus CCRT: HR, 0.743; 95% CI, 0.554–0.995; $P=0.046$) (Figure 3B). Furthermore, the ICT-CCRT arms were pooled together, and the median TTF were 13.8 (95% CI, 11.4–17.7) and 8.6 months (95% CI, 7.0–13.0) for ICT-CCRT and CCRT alone, respectively (log-rank = 0.013), with a significant benefit for ICT-CCRT versus CCRT (HR, 0.722; 95% CI, 0.560–0.931; $P=0.01$). The median OS for TPF-CCRT, PF-CCRT and CCRT were, respectively, 35.6 (95% CI, 24.2–51.4), 37.1 (95% CI, 21.9–65.2) and 29.4 months (95% CI, 18.9–45.4) (n.s.).

The ORRs at the treatment arms ranged 85.4%–91% and 81.6%–90.5%, in the ITT and PP populations, respectively (n.s.). The ORRs during ICT were from 77.7% to 80.1% (n.s.). In addition, the response pattern was different, with higher CR rates in

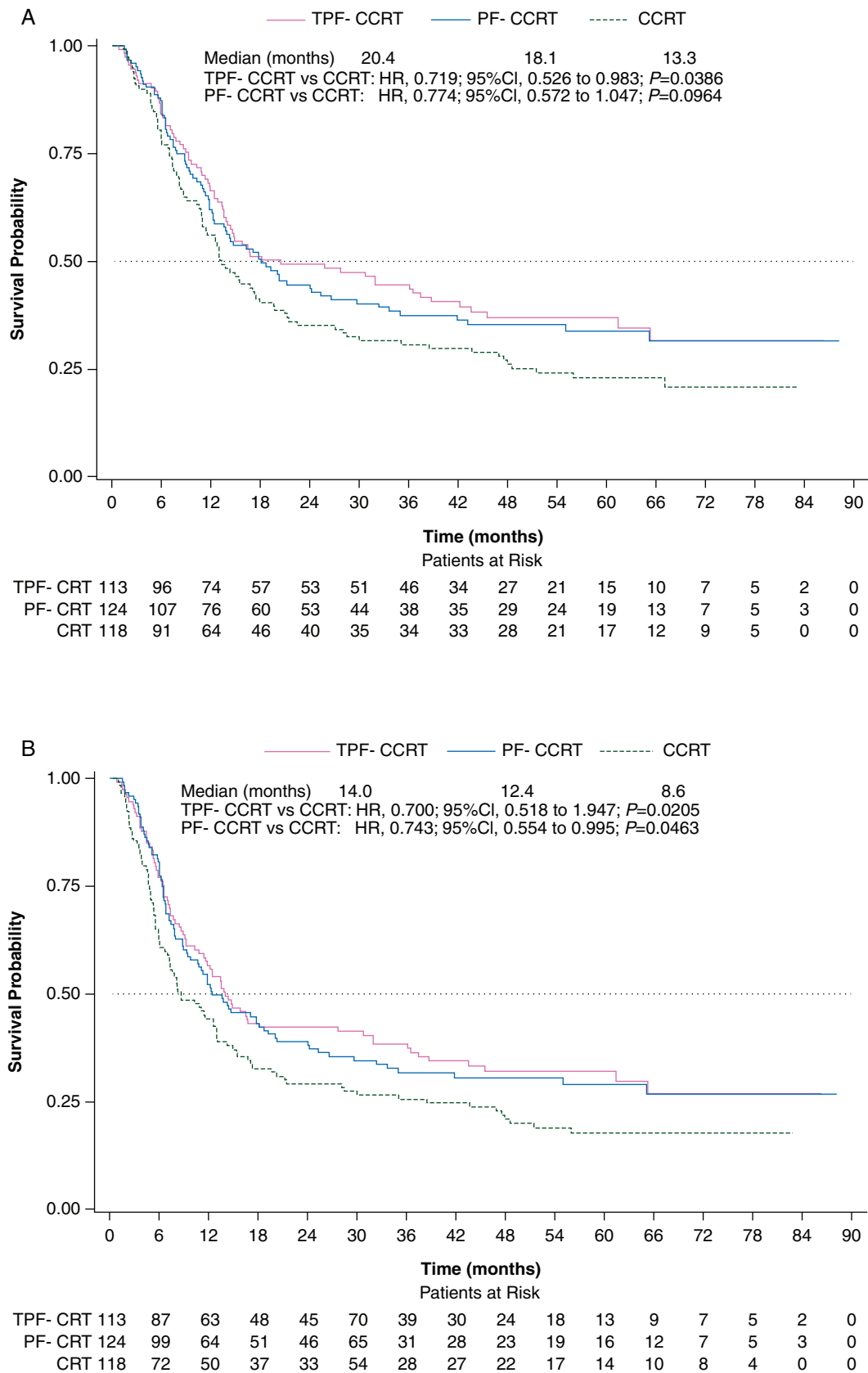


Figure 3. (A) PFS (PP population). (B) TTF (PP population).

Table 2. Grade 3 or 4 toxic effects per treatment arm

Toxicity	Induction period				Chemoradiotherapy period					
	TPF (<i>n</i> = 153)		PF (<i>n</i> = 156)		TPF-CCRT (<i>n</i> = 106)		PF-CCRT (<i>n</i> = 114)		CCRT (<i>n</i> = 118)	
	Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)	Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)	Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)	Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)	Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)
Hematologic										
Anemia	3 (2.0)	1 (0.7)	1 (0.6)	0 (0.0)	5 (4.7)	0 (0.0)	5 (4.4)	1 (0.9)	4 (3.4)	1 (0.9)
Thrombocytopenia	5 (3.3)	0 (0.0)	5 (3.2)	4 (2.6)	8 (7.6)	4 (3.8)	6 (5.3)	3 (2.6)	4 (3.4)	1 (0.9)
Neutropenia	9 (5.9)	20 (13.1)	41 (26.3)	13 (8.3)	25 (23.6)	7 (6.6)	19 (16.7)	4 (3.5)	18 (15.3)	6 (5.1)
Febrile neutropenia	6 (3.9)	20 (13.1)	1 (0.6)	2 (1.3)	4 (3.8)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)
Leukopenia	14 (9.2)	10 (6.5)	4 (2.6)	2 (1.3)	12 (11.3)	4 (3.8)	14 (12.3)	1 (0.9)	11 (9.3)	3 (2.5)
Non-hematologic										
Venous thrombosis	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	12 (7.8)	2 (1.3)	18 (11.5)	5 (3.2)	42 (39.6)	10 (9.4)	45 (39.5)	12 (10.5)	34 (28.8)	5 (4.2)
Nausea	5 (3.3)	0 (0.0)	2 (1.3)	0 (0.0)	3 (2.8)	0 (0.0)	4 (3.5)	0 (0.0)	5 (4.2)	1 (0.9)
Vomiting	9 (5.9)	1 (0.7)	3 (1.9)	0 (0.0)	5 (4.7)	0 (0.0)	4 (3.5)	0 (0.0)	8 (6.8)	2 (1.7)
Nephropathy	8 (5.2)	2 (1.3)	2 (1.3)	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.8)	0 (0.0)	5 (4.2)	1 (0.9)
Infection	5 (3.3)	2 (1.3)	3 (1.9)	0 (0.0)	4 (3.8)	1 (0.9)	5 (4.4)	2 (1.8)	4 (3.4)	1 (0.9)
Diarrhea	9 (5.9)	2 (1.3)	5 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Asthenia	15 (9.8)	1 (0.7)	8 (5.1)	0 (0.0)	7 (6.6)	0 (0.0)	7 (6.1)	0 (0.0)	4 (3.4)	0 (0.0)
Alopecia	3 (2.0)	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.9)	0 (0.0)	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.7)	0 (0.0)	14 (11.3)	2 (1.8)	9 (7.6)	0 (0.0)
Hypokalemia	5 (3.3)	2 (1.3)	2 (1.3)	2 (1.3)	0 (0.0)	1 (0.9)	1 (0.9)	2 (1.8)	2 (1.7)	1 (0.9)
Hyponatremia	7 (4.6)	1 (0.7)	6 (3.9)	1 (0.6)	3 (2.8)	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Decreased appetite	8 (5.2)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.9)	0 (0.0)	7 (6.1)	1 (0.9)	2 (1.7)	0 (0.0)
Odynophagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (13.2)	0 (0.0)	17 (14.9)	0 (0.0)	8 (6.8)	0 (0.0)
Dysphagia	2 (1.3)	0 (0.0)	2 (1.3)	0 (0.0)	9 (8.5)	0 (0.0)	6 (5.3)	0 (0.0)	5 (4.2)	0 (0.0)
Ototoxicity	1 (0.7)	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Neurotoxicity	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.9)	0 (0.0)	3 (2.6)	0 (0.0)	2 (1.7)	0 (0.0)
Other	28 (18.4)	12 (7.8)	26 (16.9)	4 (2.6)	27 (25.2)	2 (1.8)	32 (27.0)	7 (6.1)	32 (27.2)	5 (4.5)

the ICT-CCRT arms compared with CCRT alone (supplementary Table S1, available at *Annals of Oncology* online).

The LRC proportion in the ITT population was very similar across treatment arms (TPF-CCRT: 52.9%, *n* = 82; PF-CCRT: 51.3%, *n* = 81 and CCRT: 49.2%, *n* = 63; *P* = 0.8279). Within the PP population, the proportion of LRC was significantly higher for ICT-CCRT than for CCRT (*P* = 0.02). The LRC rates were 68.1% (*n* = 77), 62.1% (*n* = 77) and 51.7% (*n* = 61) at TPF-CCRT, PF-CCRT and CCRT arms, respectively (*P* = 0.03).

Elective residual tumor resections, allowed after CCRT, were less frequent in ICT-CCRT than in CCRT [ITT: n.s.; TPF-CCRT: 42 (27.1%); PF-CCRT: 48 (30.8%) and CCRT alone: 45 (35.2%)].

adverse events

All treated patients presented at least one adverse event during the trial. Grade 3 adverse events were roughly four times more common than grade 4.

The most reported grade 3–4 hematologic adverse events was neutropenia and the most reported non-hematological adverse events included stomatitis, asthenia, odynophagia, vomiting and rash.

During ICT, grade 3–4 febrile neutropenia was more frequent in the TPF arm (17.0%) than in the PF arm (1.9%), and grade 3–4 leukopenia was also higher in the TPF arm (TPF, 15.7%; PF,

3.9%). However, the rate of grade 3–4 non-febrile neutropenia was higher for PF (34.6%) than TPF (19.0%). The introduction of prophylactic G-CSF for patients allocated to TPF reduced the grade 3–4 febrile neutropenia rate (22.5% versus 15.9%). Of note, the infection rates in TPF and PF were rather similar. During CCRT, grade 3–4 neutropenia was more frequent in the TPF-CCRT arm than in the PF-CCRT and CCRT arms. Both odynophagia and stomatitis of grade 3–4 were higher during CCRT in both ICT-CCRT arms than in the CCRT alone arm. Grade 3–4 ototoxicity was present in all treatment arms and periods (0.7% to 1.3%). Grade 3–4 nephropathy, also reported in all groups, was higher at TPF-CCRT (8.4%), during ICT with TPF (6.5%), and CCRT alone arms (5.1%). During CCRT, neurotoxicity was more frequent in both PF-CCRT (2.6%) and CCRT alone (1.7%) treatment arms than in TPF-CCRT group (0.9%) (Table 2).

Thirteen deaths due to study treatment toxicity were reported, seven in TPF-CCRT arm; four in PF-CCRT arm and two in CCRT arm, mainly by febrile neutropenia before G-CSF was implemented.

discussion

This trial in unresectable LASCCHN is the first, to our knowledge, to compare TPF-CCRT, PF-CCRT and CCRT.

Overall, ICT-CCRT did not evidence a significant efficacy advantage over CCRT.

Regarding the differences between the ITT and PP analyses, 45 patients from the TPF-CCRT arm, and 33 from the PF-CCRT arm, did not receive CCRT for reasons other than disease progression.

Although PFS and TTF times were either similar or higher for TPF compared with PF, the differences were non-significant. The non-advantage of TPF over PF does not agree with previous trials of ICT-CCRT or ICT-RT, with larger samples than ours of patients treated with TPF and PF [10, 11].

The median PFS in the PP population showed a significant benefit for TPF-CCRT over CCRT alone. Although it was non-significant, the median PFS for PF-CCRT was also higher than that for CCRT. These results suggest that ICT could be of benefit to selected patients.

In addition, OS values from ITT patients were very similar across all treatment arms. Regarding this issue, both the median PFS and median OS for both TPF-CCRT and PF-CCRT were higher to those reported by Vermorken et al. [11]. In that trial, TPF-RT significantly increased both PFS and OS in comparison to those observed with PF-RT. In this regard, the improvement of OS has not been conclusively proven in some trials [12].

An important proportion of patients failed to ICT due to toxicity and, in this regard, most patients had ECOG 1 and their tumors were mainly T4. In contrast, in previous ICT trials, the proportion of patients with ECOG 0 was higher than those with ECOG 1, and T4 tumors were less frequent than in this trial [10, 11]. The importance of ECOG status is highlighted by post-hoc analysis, which showed, for ICT-CCRT treated patients (ITT population), median PFS, TTF and OS of 26.6, 14.4 and 43.6 months, respectively, in ECOG 0 patients, while the corresponding ones in ECOG 1 patients were 12.4, 6.8 and 20.0 months. The lower proportion of elective residual tumor resections, in ICT-CCRT versus CCRT, could partially explain the efficacy results and reflect the benefit of ICT-CCRT over CCRT. This is in line with results from Paccagnella et al. [13]. The absence of the standard criteria for unresectability complicates the study of unresectable LASSCHN. Furthermore; age, performance status and patient's willingness affect resectability [14]. In the Vermorken's trial, neck dissection was considered for all patients before and 3 months after RT [11].

The prevalence of human papillomavirus (HPV) in head and neck cancer is roughly 26% [15]. HPV status, a prognostic factor in head and neck cancer, was unknown in our trial and could be a confounding factor.

The expected higher proportion of febrile neutropenia in the TPF arm was controlled with prophylactic G-CSF, and the rate of toxicity-related deaths was within the expected range [12].

In conclusion, this trial failed to show advantage of ICT-CCRT over CCRT alone in unresectable LASSCHN.

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The following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article.

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Consultant or advisory role. Entity: Sanofi-Aventis. Relationship: Myself. Compensation: Compensated.

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Adherence to consensus-based diagnosis and treatment guidelines in adult soft-tissue sarcoma patients: a French prospective population-based study[†]

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Background: Soft-tissue sarcomas (STSs) are rare tumors with varied histological presentations. Management and treatment are thus complex, but crucial for patient outcomes. We assess adherence to adult STS management guidelines across two French regions (10% of the French population). We also report standardized incidence.

Patients and methods: STS patients diagnosed from 1 November 2006 to 31 December 2007 were identified from pathology reports, medical hospital records, and cancer registries. Guideline adherence was assessed by 23 criteria (validated by Delphi consensus method), and age and sex-standardized incidence rates estimated. Associations between patient, treatment, and institutional factors and adherence with three major composite criteria relating to diagnostic imaging and biopsy as well as multidisciplinary team (MDT) case-review are reported.

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