

Taxane-Cisplatin-Fluorouracil As Induction Chemotherapy in Locally Advanced Head and Neck Cancers: An Individual Patient Data Meta-Analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group

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See accompanying editorial on page 2844

A B S T R A C T

Purpose

Cisplatin plus fluorouracil (PF) induction chemotherapy has been compared with taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil (Tax-PF) in randomized trials in locoregionally advanced head and neck cancers (LAHNCs). The aim of this meta-analysis was to study the efficacy and toxicity of Tax-PF and PF and identify differences in outcomes in subsets of patients.

Methods

Five randomized trials representing 1,772 patients were identified. Updated individual patient data (IPD) were retrieved for all trials. The log-rank test, stratified by trial, was used for comparison. Interaction or trend tests were used to study the interaction between covariates and treatment.

Results

Median follow-up was 4.9 years. The hazard ratio (HR) of death was 0.79 (95% CI, 0.70 to 0.89; $P < .001$; absolute benefit at 5 years: 7.4%) in favor of Tax-PF. Heterogeneity was significant ($P = .08$, $I^2 = 51\%$) and related to one trial. There was no more heterogeneity after exclusion of this trial ($P = .99$, $I^2 = 0\%$), and HR of death was 0.72 (95% CI, 0.63 to 0.83) in favor of Tax-PF. There was no interaction between treatment effect and the following patient covariates: age, sex, performance status, tumor stage, or site. Tax-PF was associated with significant reductions of progression, locoregional failure, and distant failure compared with PF, with HRs of 0.78 (95% CI, 0.69 to 0.87; $P < .001$), 0.79 (95% CI, 0.66 to 0.94; $P = .007$), and 0.63 (95% CI, 0.45 to 0.89; $P = .009$) respectively.

Conclusion

This IPD meta-analysis shows the superiority of Tax-PF over PF as induction chemotherapy. Its precise role in the management of LAHNC remains to be determined.

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INTRODUCTION

Despite improvements in screening and changes in epidemiology, head and neck squamous cell carcinomas (HNSCCs) are frequently diagnosed at a locoregionally advanced stage.¹ Concomitant chemoradiotherapy (CRT) has been shown to improve survival and is considered a standard of care.² In the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), the addition of induction chemotherapy using cisplatin plus fluorouracil (PF) to local treatment did not decrease locoregional failures. However, it was associated with a small im-

provement in overall survival (OS; hazard ratio [HR]: 0.90; 95% CI, 0.82 to 0.99) and distant failures.² An exploratory indirect analysis of survival in the MACH-NC database has shown that CRT was superior to PF induction chemotherapy.³ Hence PF induction chemotherapy is not considered as a standard treatment in locoregionally advanced HNSCC, except in the case of larynx preservation, for which both PF induction chemotherapy and concomitant CRT are considered standard.^{4,5}

Recently, randomized trials have studied whether induction regimens comprising taxane, cisplatin, and fluorouracil (Tax-PF) could be superior

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to PF.⁶⁻¹¹ Most of them have shown a significant increase in OS and progression-free survival (PFS) in the Tax-PF arms, but the power associated with each of them prevented studying more specific end points.

Therefore, in 2008, the MACH-NC Collaborative Group launched an update of the MACH-NC database to include all taxane trials so that they could summarize their results on survival end points, pattern of failure, toxicity, and interaction between treatment effect and patient subgroups.

METHODS

Because two different taxanes have been studied in the trials, the taxane arms of the meta-analysis are named Tax-PF. The discussion is more focused on the most studied regimen, which uses docetaxel and is named TPF as in the literature.

Study Design, Search Strategy, and Study Selection

A protocol was written before data collection specifying inclusion criteria, search strategy, end points, and statistical analysis plan (Data Supplement). To be included, trials had to be randomized, include nonmetastatic patients with locoregionally advanced HNSCC treated with a curative intent, not be confounded by additional therapeutic differences between the two groups (eg, differences in chemotherapy during radiation), and had to compare Tax-PF with PF followed by radiotherapy (RT; or CRT) or to compare Tax-PF followed by RT (or CRT) with upfront CRT. Trials must have been properly randomized and have completed accrual before January 2007.

To limit publication bias, data from all published and unpublished randomized trials evaluating the preceding comparisons were sought using electronic database searching for the period 1970 through 2007 (MEDLINE, Cancerlit, DARE, Embase, CCT meta-register), hand searching (review articles, meeting proceedings), and by contacting experts in the field and members of the meta-analysis collaborative group.

Data Collection

The data collected for each patient were age, sex, performance status, tumor site, histology, stage, allocated treatment, and date of randomization, compliance with induction, and concomitant chemotherapy. Data on OS, PFS, pattern of failure, cause of death, and acute and late toxicities were sought for all patients, including patients excluded from the trial analysis. Survival status was updated whenever possible.

All data were checked for internal consistency and compared with each trial protocol and published reports. Standard checks included quantification of missing data, errors in dates, and data validity, in addition to consistency assessment. Randomization integrity was assessed by checking patterns of treatment allocation and balance of baseline characteristics by treatment group. Follow-up of patients was checked to ensure that it was balanced between treatment groups.¹² Each trial was analyzed individually, and these analyses were sent to the trialists for review and validation.

Statistical Analysis

The main end point was OS, defined as the time from randomization until death from any cause. PFS (defined as the time from randomization until first progression or death from any cause), cumulative locoregional failure (LRF), and distant failure (DF) were secondary end points, as were cancer and noncancer mortality (Data Supplement). For LRF analysis and DF analysis, patients who experienced first a DF or an LRF were censored at the time of the first failure. When both a local and a distant failure occurred at the same time, the patient was counted as a distant failure. In a post hoc analysis, overall mortality 120 days after randomization was used as a proxy for induction chemotherapy related death. The 120 days cutoff was chosen because most of the patients started RT between day 90 and day 120.

All analyses were prespecified in the protocol and performed on an intention-to-treat basis. The meta-analysis had 80% power to detect an OS difference of 6% at 5 years. Survival analyses were stratified by trial, and the

log-rank observed minus expected number of death ($O - E$) and its variance were used to calculate individual and overall HR, with a fixed effect model.¹³ χ^2 tests and I^2 were used to study heterogeneity between trials.^{14,15} Median follow-up for all patients was calculated with the reverse Kaplan-Meier method.¹⁶ To study the interaction, an analysis stratified by trial was performed for each covariate group, and the corresponding HRs were compared by a test for interaction or trend. Stratified survival curves were used to calculate absolute difference at 5 years.¹⁴ Stewart's method was used to compute absolute benefit according to subgroup in the absence of significant interaction.¹⁷ P values were two sided. Statistical analyses were performed using Statistical Analysis Systems software, version 9.2, for Microsoft Windows (SAS Institute, Cary, NC).

RESULTS

Description of the Trials

The meta-analysis flowchart is presented in the Data Supplement. Six trials fulfilled the inclusion criteria.^{6-11,18} Among them, four compared Tax-PF with PF induction chemotherapy, one compared Tax-PF induction with no induction chemotherapy, and one was a three-arm trial comparing Tax-PF, PF, and no induction. Overall, five trials (1,772 patients) were available for the Tax-PF versus PF comparison,^{6-8,10,11,18} and two were available for the Tax-PF versus no induction meta-analysis (384 patients).^{7,9} This latter meta-analysis was not performed because of the limited number of trials and patients, and because one trial⁷ contributed to more than 75% of the patients. A description of the trials is provided in the Data Supplement. Patient follow-up was updated for all trials for the purpose of this meta-analysis. Median follow-up was 4.9 years (interquartile range, 3.1 to 6.7 years).

Tax-PF Versus PF Meta-Analysis

Description of the patients. Overall, 1,772 patients, representing 98% of the potentially eligible patients, were included in the meta-analysis, of whom 89 had been excluded in the initial trial publications or presentations (Data Supplement). Patient characteristics are detailed in the Data Supplement. Most of the patients were male (90%) and had a performance status of 0 or 1 (99%). Most tumors were locally advanced (T3-T4, 85%; N2-3, 62%). Thirty-nine percent of the tumors arose in the oropharynx and 25% in the hypopharynx. The mean age of the patients was 56 years in both groups.

OS and PFS. The causes of deaths ($n = 1,029$) and the types of events for PFS ($n = 1,162$) are provided in the Data Supplement. Tax-PF induction chemotherapy improved OS as compared with PF induction chemotherapy, with an HR of death of 0.79 (95% CI, 0.70 to 0.89; $P < .001$) and an absolute benefit at 5 years of 7.4%, from 35.0% to 42.4% (Fig 1A). Tax-PF induction chemotherapy also improved PFS, with an HR of 0.78 (95% CI, 0.69 to 0.87; $P < .001$) and an absolute benefit at 5 years of 7.1%, from 28.4% to 35.5% (Fig 1B). A between trial heterogeneity was observed for the OS analysis with an I^2 value of 51% ($P = .08$), but not for PFS. This heterogeneity was related to the Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC) 2002 trial (Fig 2).

Locoregional-distant failure. Data on the type of failure were not available for the Spain 1998 trial,⁶ for 89 patients (25%) of the European Organisation for Research and Treatment of Cancer trial,¹¹ and for 93 patients (30%) of the TTCC 2002 trial⁷; therefore, locoregional

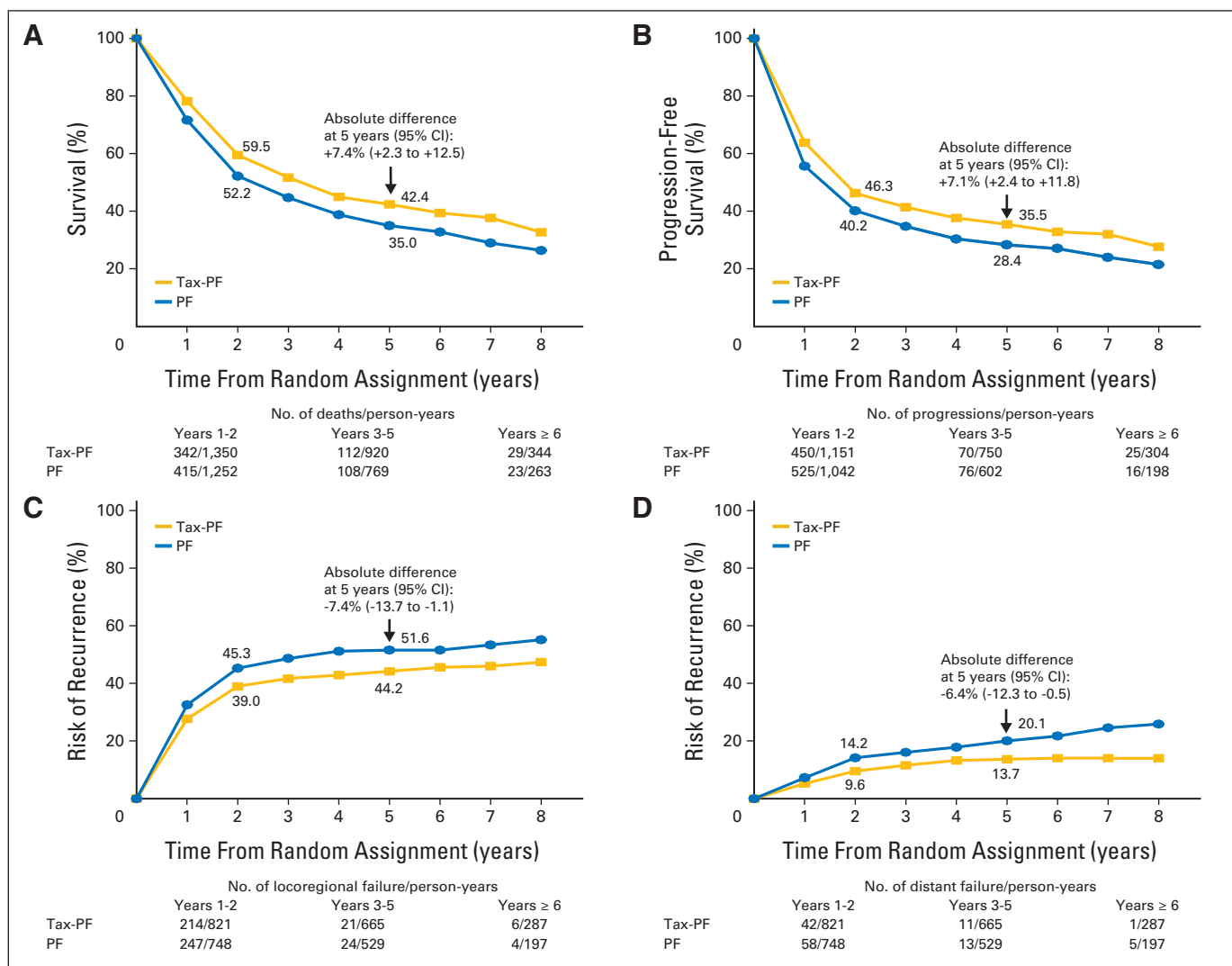


Fig 1. Survival curves for (A) overall survival, (B) progression-free survival, (C) locoregional failure, and (D) distant failure. PF, cisplatin, fluorouracil; Tax-PF, taxane, cisplatin, fluorouracil.

and distant failure analyses were conducted without these patients. Tax-PF induction chemotherapy was associated with a lower rate of locoregional failures than PF, with an HR of 0.79 (95% CI, 0.66 to 0.94; $P = .007$) and an absolute decrease of locoregional failures of 7.4% at 5 years, from 51.6% to 44.2% (Fig 1C). Tax-PF induction chemotherapy was associated with a lower rate of distant failures than PF, with an HR of 0.63 (95% CI, 0.45 to 0.89; $P = .009$) and an absolute decrease of distant failures of 6.4% at 5 years, from 20.1% to 13.7% (Fig 1D). There was no heterogeneity between trials for the locoregional and distant failure analyses (Fig 3).

Head and neck cancer and noncancer mortality. All trials (patients) were included in this analysis, and the types of events are described in the Data Supplement. The observed difference in OS was related to a reduction of head and neck cancer mortality in favor of the Tax-PF arms (HR = 0.74; 95% CI, 0.65 to 0.84; $P < .001$), with an absolute difference at 5 years of 9.3%, from 60.1% to 50.8% (Data Supplement). No difference in head and neck noncancer mortality was observed (HR = 1.12; 95% CI, 0.82 to 1.51; $P = .47$). For the last

end point, there was a significant heterogeneity, with an I^2 equal to 60% (Data Supplement).

Treatment compliance and toxicity. The hazard ratio of mortality 120 days after randomization was 0.91 (95% CI, 0.62 to 1.33; $P = .62$), showing a nonsignificant reduction in the risk of early death in favor of Tax-PF. The observed heterogeneity ($P = .03$, $I^2 = 64%$) was related to one trial⁷ in which a significant increase of early deaths in the Tax-PF arm was observed (HR = 2.53; 95% CI, 1.15 to 5.54; Data Supplement).

Of the 1,772 patients included, 1,757 (99%) have received at least one cycle of induction chemotherapy, and 1,459 have received the induction chemotherapy as planned (83%, Tax-PF: 85%, PF: 81%, $P = .04$; Data Supplement). Concomitant chemotherapy was planned in three trials (1,194 patients). Compliance with concomitant chemotherapy was significantly different between Tax-PF and PF for trials with planned CRT, with more patients able to receive the concomitant chemotherapy as planned in the Tax-PF arms and fewer patients not receiving any chemotherapy at all (49% v 43% and 31% v 38%

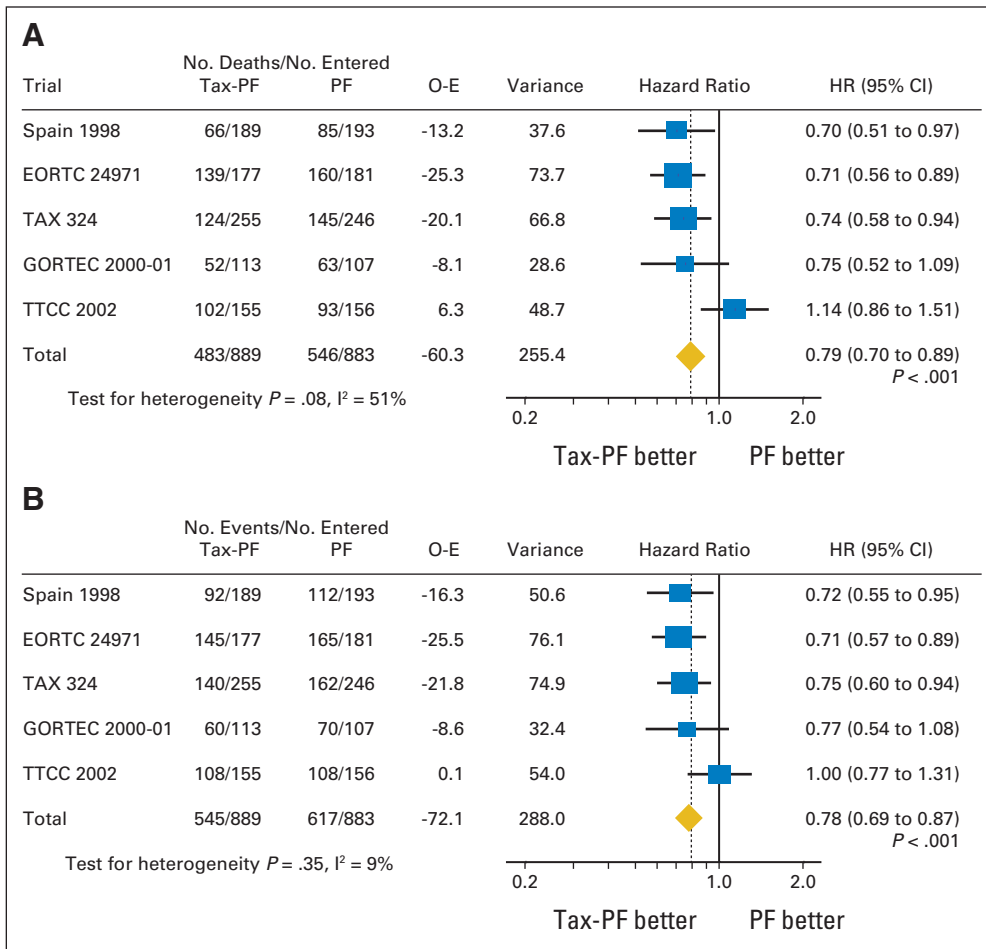


Fig 2. Forest plots for (A) overall survival and (B) progression-free survival. Each trial is represented by a square, the center of which denotes the hazard ratio (HR) for that trial, with the horizontal lines showing the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The gold diamonds represent pooled HRs for the overall HRs, with the center denoting the HR and the extremities the 95% CI. The fixed effect model was used. EORTC, European Organisation for Research and Treatment of Cancer; GORTEC, Groupe d'Oncologie Radiothérapie Tête et Cou; O-E, observed minus expected deaths or events; PF, cisplatin, fluorouracil; TAX, Taxotere (docetaxel; sanofi-aventis, Bridgewater, NJ); Tax-PF, taxane, cisplatin, fluorouracil; TTCC, Grupo Español de Tratamiento de Tumores de Cabeza y Cuello.

respectively, $P = .02$; Data Supplement). Compliance with RT was significantly better in the Tax-PF arms, with 73% starting the planned RT versus 67% in the PF arms ($P = .004$; Data Supplement). No data on tumor response was collected. It is possible that this difference is attributable to the higher response rate to TPF, and therefore, by protocol, fewer patients in the PF treatment groups would be candidates for RT and/or concomitant treatment. Among patients who did start chemoradiotherapy, there was no difference in compliance with concomitant chemotherapy ($P = .51$, Data Supplement). Of note, the TTCC trial has the largest difference between planned RT duration and observed value, which could partly explain the differences in outcome between this trial and the others.

Among the four analyzed toxicities (data missing for the Spain 1998 trial), only grade 3 to 4 neutropenia and thrombocytopenia were significantly different between the two groups ($P < .001$; Data Supplement), with heterogeneity between trials explained by the TTCC 2002 trial. The high number of missing values limits conclusion regarding the toxicity patterns of Tax-PF versus PF.

Subgroup and sensitivity analyses. In the end points for which heterogeneity was observed, the TTCC 2002 trial was the outlier. After the exclusion of this trial as a sensitivity analysis, heterogeneity was not significant anymore ($I^2 = 0\%$ for OS and for PFS). The HR for OS and PFS respectively became 0.72 (95% CI, 0.63 to 0.83; $P < .001$) and 0.73 (95% CI, 0.65 to 0.83; $P < .001$). The HRs for all end points with and

without TTCC 2002 trial are reported in Table 1. Because of the heterogeneity related to the TTCC 2002 trial, subgroup analyses were performed without this trial. There was no interaction between patient age, performance status, patient sex, tumor stage, or location and either OS or PFS (Data Supplement). An unplanned post hoc analysis showed no interaction between N stage (N0-1 v N2-3) and treatment effect on distant metastases ($P = .79$). This was foreseeable because of the small number of distant relapses as first site of relapse.

DISCUSSION

This individual patient data meta-analysis of Tax-PF induction chemotherapy shows that Tax-PF significantly improves OS, PFS, head and neck cancer mortality, and locoregional and distant failure compared with PF for locally advanced HNSCC. Tax-PF is also associated with a better compliance with induction chemotherapy. More patients in the Tax-PF group proceeded to concomitant chemoradiotherapy, likely reflecting the higher response rates.^{6,10,11} The compliance with subsequent chemotherapy based on those initiating such treatment was not different.

These data are in agreement with previous reports^{6,10,11,18} and allow to precisely estimate the magnitude of the benefit of Tax-PF compared with PF. The strengths of the meta-analysis are related to its

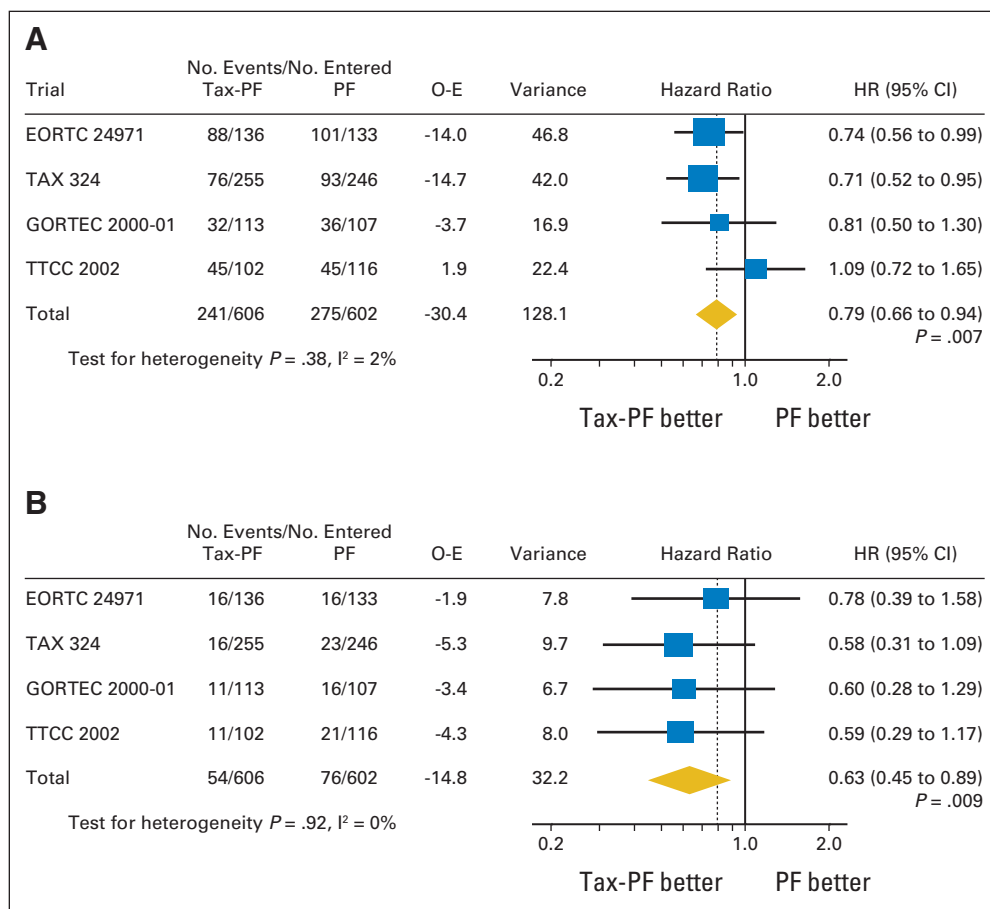


Fig 3. Forest plots for (A) locoregional failure and (B) distant failure. The analyses are performed only for four trials, as the pattern of relapse was not available for the Spain 1998 trial. EORTC, European Organisation for Research and Treatment of Cancer; GORTEC, Groupe d'Oncologie Radiothérapie Tête et Cou; HR, hazard ratio; O-E, observed minus expected deaths or events; PF, cisplatin, fluorouracil; TAX, Taxotere (docetaxel; sanofi-aventis, Bridgewater, NJ); Tax-PF, taxane, cisplatin, fluorouracil; TTCC, Grupo Español de Tratamiento de Tumores de Cabeza y Cuello.

rigorous methodology. The limitations of the analysis are mostly related to the heterogeneity of trials and missing data. Indeed these trials included different induction chemotherapy regimens, patient characteristics, tumor subsites and local extensions (resectable ν unresectable), or treatment settings (organ preservation ν definitive treatment). First, the meta-analysis includes two types of Tax-PF regimens using different taxanes: docetaxel^{7,8,10,11,18} or paclitaxel.⁶ However, the benefit of Tax-PF does not seem to vary with the taxane used (Fig 2). Second, one trial was a larynx preservation trial,¹⁰ which is a different setting compared with locally advanced HNSCC. Third, one trial had a short follow-up and no data on the type of relapse.⁶ Fourth, one trial had heterogeneous survival results compared with the others.⁷ In this trial, Tax-PF was associated with a significant increase in 120-day mortality (Data Supplement) and non-head and neck cancer mortality (Data Supplement). This trial's protocol was amended to include systematic granulocyte colony-stimulating factor (G-CSF) prophylaxis with Tax-PF, which resulted in a decrease of early deaths and an increase in OS in the Tax-PF arm (HR for OS: 1.36 [95% CI, 0.98 to 1.89] without systematic G-CSF and 0.64 [95% CI, 0.36 to 1.13] with systematic G-CSF). The absence of interaction between trial or patients' characteristics and treatment effect prevents from defining a specific population that would not benefit from Tax-PF induction. Finally, the number of missing data regarding the type of relapse must be discussed (one trial with no data,⁶ two with incomplete data^{7,11}). Because there was no difference regarding tumor location, T stage, or

N stage between patients with/without complete data, and no difference regarding treatment effect on OS in these two populations, we believe that these incomplete data reduce the power of the analysis but do not bias it.

Whether Tax-PF induction chemotherapy followed by RT could be considered standard for locally advanced HNSCC cannot be answered by this meta-analysis. We discuss pros and cons regarding this important issue. First, Tax-PF and especially TPF (docetaxel-PF) have shown a marked improvement as compared with PF. In the present analysis, Tax-PF induction improved OS by 7.4% at 5 years, which is of the same magnitude as the survival benefit of concomitant CRT in the MACH-NC analysis (6.5% at 5 years), although the latter meta-analysis included a larger number of patients and trials.² Tax-PF induction was also associated with a significant reduction of both local and distant failures compared with PF. Considering that in the MACH-NC analysis, PF induction was not associated with a difference in terms of locoregional control,² one could speculate based on indirect comparisons that TPF induction would be superior to RT alone in terms of locoregional control.

There are also several reasons to consider that concomitant CRT has to remain the standard treatment in locoregionally advanced HNSCC. First, there is no evidence from randomized trials suggesting that Tax-PF followed by RT (\pm concomitant chemotherapy) is superior to concomitant CRT. Second, the decrease in locoregional failure

Table 1. Summary of Efficacy End Points With or Without TTCC 2002 Trial

Value	Overall Survival	Progression-Free Survival	Locoregional Failure	Distant Failure	Cancer Deaths	Noncancer Deaths	120-Day Mortality
All trials							
No. of events	1,029	1,162	516	130	861	168	105
No. of patients	1,772	1,772	1,208	1,208	1,772	1,772	1,772
Hazard ratio	0.79	0.78	0.79	0.63	0.74	1.12	0.91
95% CI	0.70 to 0.89	0.69 to 0.87	0.66 to 0.94	0.45 to 0.89	0.65 to 0.84	0.82 to 1.51	0.62 to 1.33
5-year absolute difference, %	7.4	7.1	-7.4	-6.4	-9.3	1.8	-1.4
95% CI*	2.3 to 12.5	2.4 to 11.8	-13.7 to -1.1	-12.3 to -0.5	-14.7 to -3.9	-2.6 to 6.2	-3.79 to 0.99
<i>P</i>	< .001	< .001	.007	.009	< .001	.47	.62
Heterogeneity <i>P</i>	.08	.35	.38	.92	.59	.04	.03
<i>I</i> ² , %	51	9	2	0	0	60	64
Without TTCC 2002							
No. of events	834	946	426	98	713	121	80
No. of patients	1,461	1,461	990	990	1,461	1,461	1,461
Hazard ratio	0.72	0.73	0.74	0.65	0.71	0.84	0.66
95% CI	0.63 to 0.83	0.65 to 0.83	0.61 to 0.89	0.43 to 0.96	0.61 to 0.82	0.59 to 1.21	0.43 to 1.02
5-year absolute difference, %	10.1	8.9	-9.4	-5.1	-10.6	-1.8	-3.1
95% CI*	4.4 to 15.8	3.6 to 14.2	-16.3 to -2.5	-11.4 to 1.2	-16.5 to -4.7	-6.2 to 2.6	-5.65 to -0.55
<i>P</i>	< .001	< .001	.002	.03	< .001	.36	.06
Heterogeneity <i>P</i>	0.99	0.99	0.90	0.80	0.86	0.63	0.49
<i>I</i> ² , %	0	0	0	0	0	0	0

Abbreviations: PF, cisplatin, fluorouracil; TTCC, Grupo Español de Tratamiento de Tumores de Cabeza y Cuello.

*PF arm is the reference for 5-year absolute variation calculation. Five-year absolute variations are between survival rates for the overall and progression-free survival, between failure rates for locoregional failure and distant failure, and between mortality rates for cancer and noncancer deaths.

associated with Tax-PF is lower than the one associated with platinum-based concomitant CRT in MACH-NC (13.5% at 5 years).² Third, there are concerns regarding the ability to deliver optimal local treatment after Tax-PF induction, namely to add concomitant cisplatin chemotherapy to RT, or even to perform radiotherapy after induction Tax-PF (only 73% started radiotherapy in the Tax-PF arms in the present meta-analysis). Among the trials included, two used RT alone (for the EORTC trial after four cycles of TPF),^{10,11} two used concomitant cisplatin every 3 weeks,^{6,7} and one used concomitant weekly carboplatin.¹⁸ In our analysis, only 50% of patients received the concomitant chemotherapy as planned in the Tax-PF arms. This is comparable with the TREMPIN larynx preservation randomized trial,¹⁹ in which only 43% of the patients received concomitant cisplatin as planned after induction TPF. Then a major and unanswered issue is whether intensifying induction treatment could jeopardize the efficacy of concomitant CRT or if the systemic and local benefits of Tax-PF are sufficient to allow better disease control by themselves without concomitant chemotherapy.

The further positioning of Tax-PF as standard treatment will come from randomized trials directly comparing Tax-PF induction followed by concomitant CRT with upfront concomitant CRT. Such direct trials have been performed. The data of two trials had been retrieved for this meta-analysis (the TPF v PF arm of the second one is included in this meta-analysis).^{7,9} They do not show a significant difference between the arms, but one is a phase II trial⁹ and the other⁷ has to be considered with caution because it is responsible for the heterogeneity observed in this meta-analysis. Two other randomized trials have recently been presented.^{20,21} One is potentially confounded as the CRT regimens are different between the two arms.²¹ The other has used a nonstandard split course bifractionated docetaxel-hydroxyurea-based CRT regimen.²⁰ None showed an appreciable

trend in favor of adding upfront TPF before CRT, although the statistical power is low as a result of early termination of accrual in both trials. One of these trials focusing only on patients with N2-N3 disease showed a significant reduction of distant metastases with induction TPF.²⁰ Ongoing trials might add to the confusion, as some use different concomitant treatments (NCT01233843) or add a second randomization regarding concomitant treatment (chemotherapy v cetuximab; NCT01086826). TPF induction must be considered as one of the standards for larynx preservation,¹⁰ but further testing in patients at high risk for distant metastases (eg, those with N2-N3 disease) is merited.

Although induction Tax-PF is superior to PF in terms of OS, PFS, and locoregional and distant control, its precise role compared with upfront CRT in the management of locoregionally advanced HNSCC remains to be defined.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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Appendix

Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group

The steering committee reviewed the protocol, the results during the investigator meeting, and the manuscript. The investigators contributed to the provision of data, the validation of the reanalysis of their trial, the critical interpretation of the results during the investigator meeting, and the revision of the manuscript.

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