

LETTER TO THE EDITOR

Phase III trial of docetaxel cisplatin 5-fluorouracil induction chemotherapy for resectable oral cancer suggests favorable pathological response as a surrogate endpoint for good therapeutic outcome

Dear Editor,

Induction chemotherapy has been utilized for decades in locally advanced head and neck squamous cell carcinoma (HNSCC). The docetaxel, cisplatin, 5-fluorouracil (TPF) regimen is the most recommended induction chemotherapy regimen for HNSCC and oral squamous cell carcinoma (OSCC) [1]. However, our initial phase III trial failed to demonstrate a significant survival benefit of TPF induction chemotherapy in patients with locally advanced OSCC [2].

Although the efficacy of TPF induction chemotherapy on the overall prognosis on locally advanced OSCC patients is unclear, it is highly possible that a subset of patients could still obtain better outcomes when treated with TPF induction chemotherapy. As favorable pathological response (FPR) has been considered the most reliable prognostic predictor of induction chemotherapy since the last decade [3], it could be crucial to further confirm whether FPR after induction chemotherapy could predict the survival benefit of OSCC patients. We herein report the final results of our TPF induction chemotherapy trial and evaluate its predictive value in OSCC patients.

As previously described [2], 256 locally advanced (T1-2N1-2M0 or T3-4N0-2M0 according to the Union for International Cancer Control [2002]) OSCC patients were enrolled in this prospective, open-labeled, randomized

phase III trial. Briefly, after randomization, patients in the experimental group received TPF induction chemotherapy (docetaxel 75 mg/m² and cisplatin 75 mg/m² intravenously on day 1, followed by 5-fluorouracil 750 mg/m² per day as a 120-hour continuous intravenous infusion on days 1 to 5; every 3 weeks for two cycles) followed by surgery then postoperative radiotherapy; those in the control group received upfront surgery then postoperative radiotherapy. No concurrent postoperative chemotherapy was administered (Supplementary materials and methods).

Nine out of 256 patients (3.5%) were lost to follow-up. At the time of data cutoff in April 2020, the median follow-up time was 131 months (63 - 144 months). In total, the estimated 10-year overall survival (OS) rate was 53.9%, disease-specific survival (DSS) was 62.1%, disease-free survival (DFS) rate was 46.9%, locoregional recurrence-free survival (LRFS) rate was 48%, and distant metastasis-free survival (DMFS) rate was 53.9%. The locoregional recurrence rate in the experimental group and control group was 32.8% (42/128) and 39.1% (50/128), and the distant metastasis rate was 7.8% (10/128) and 12.5% (16/128), respectively. There was no significant difference in 10-year OS (56.3% versus 51.6%), DSS (64.1% versus 60.2%), DFS (50.8% versus 43.0%), LRFS (50.8% versus 45.3%), or DMFS rate (57.0% versus 50.8%) between patients in the experimental and control groups.

Subgroup survival analysis according to baseline characteristics showed no significant benefit of TPF induction chemotherapy in all selected subgroups except for the clinical N2 subgroup; for whom TPF induction chemotherapy could significantly improve the OS, DSS, and DMFS (but not DFS and LRFS), compared to the control group (Supplementary Table 1, Supplementary Figure 1).

In the experimental group, 119 out of 128 patients (92.9%) underwent postoperative pathological assessment

Abbreviations: AEs, adverse events; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; FPR, favorable pathological response; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR, hazard ratios; LRFS, locoregional recurrence-free survival; MPR, major pathological response; NCI/CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; OS, overall survival; OSCC, oral squamous cell carcinoma; pCR, pathological complete response; PF, cisplatin, 5-fluorouracil; TPF, docetaxel, cisplatin, 5-fluorouracil; UICC, Union for International Cancer Control

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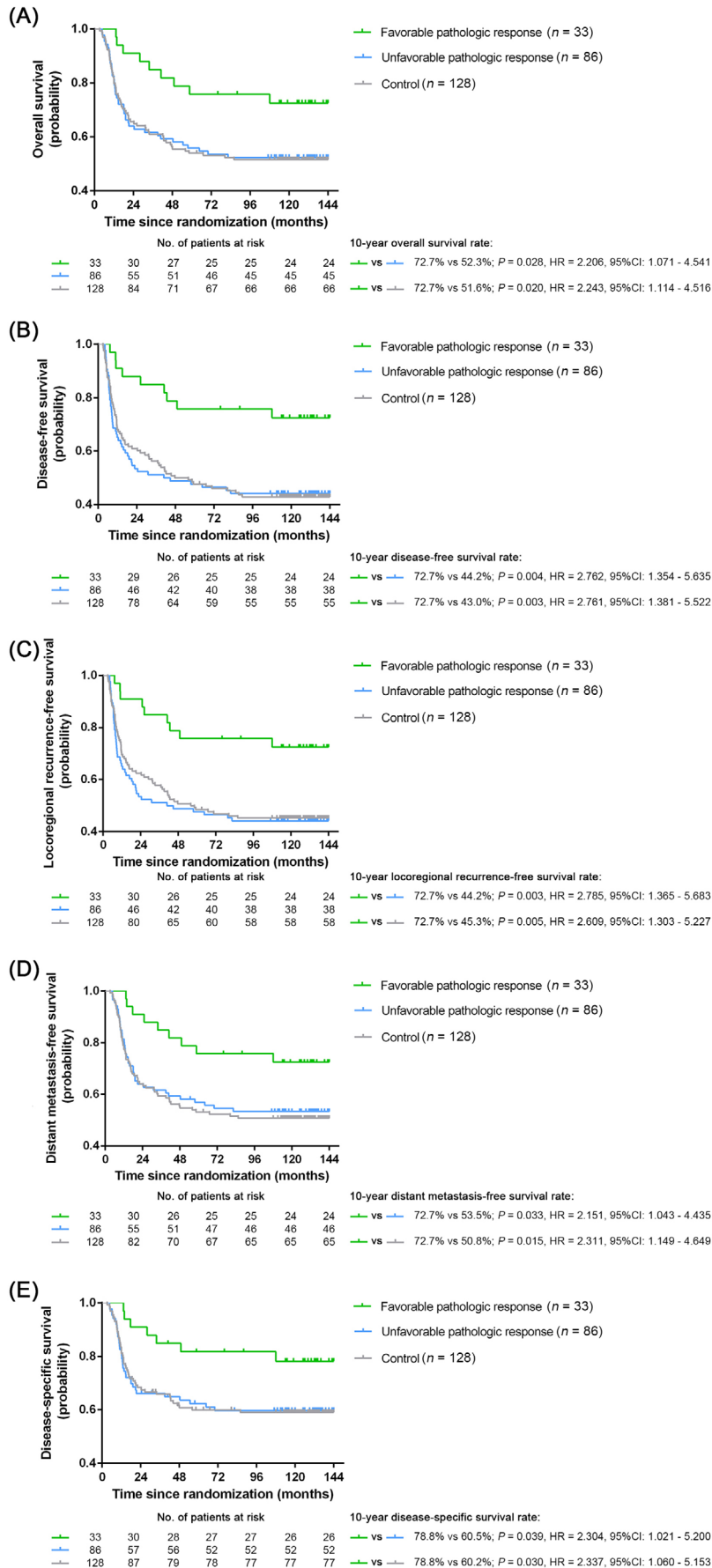


FIGURE 1 Kaplan-Meier survival curves representing the 10-year (A) overall survival, (B) disease-free survival, (C) locoregional recurrence-free survival, (D) distant metastasis-free survival, and (E) disease-specific survival of locally advanced OSCC patients with favorable and unfavorable pathological responses in the experimental group (TPF induction chemotherapy followed by surgery then postoperative radiotherapy), and patients in the control group (surgery followed by postoperative radiotherapy). OSCC: oral squamous cell carcinoma. TPF: docetaxel, cisplatin, 5-fluorouracil

(2 patients refused any treatment, 5 patients refused induction chemotherapy or surgery, 2 patients died during the period of induction chemotherapy). FPR after TPF induction chemotherapy was observed in 33 out of 119 patients (27.7%), of whom 16 patients (13.4%) had pCR. Patients with FPR after TPF induction chemotherapy had significant survival improvement compared to those without FPR after induction chemotherapy or those in the control group (Figure 1). There was no significant difference in baseline characteristics between patients with and without FPR after induction chemotherapy.

The secondary primary tumor rate was 4.7% (6/128) and 7.8% (10/128) in the experimental and control group, respectively. There was no significant difference in secondary primary tumor rates between the two groups (4.7% in the experimental group, 7.8% in the control group) or between patients with and without FPR (9.1% with FPR, 3.5% without FPR). For the late adverse events (AEs; occurred at least 3 months after the end of treatment), the most frequent were dysphasia and dysphagia, and no severe late AEs were found during the follow-up period of the patients.

Our results are in line with previously published results in OSCC [4]. In our subgroup analysis, OS, DSS, and DMFS were improved through TPF induction chemotherapy in clinical N2 patients, while DFS and LRFS were not significantly improved, indicating that the survival improvement was mainly due to the control of distance metastasis, and TPF induction chemotherapy could be possibly more suitable for patients with a higher clinical N stage. However, in another trial, adding induction chemotherapy before chemoradiotherapy did not translate into improved OS compared with chemoradiotherapy alone in patients with N2–N3 HNSCC [5]. Due to the limited sample size of the clinical N2 group, our retrospective subgroup analyses were not sufficient to guide further treatment plan until further demonstrated by convincing studies.

Besides clinical indicators, we also focused on the predictive effect of pathological response after induction chemotherapy. Patients who underwent TPF induction chemotherapy in this present study showed modest pCR (13.4%) and FPR rates (27.7%). The pCR rate was consistent with another trial investigating split TPF induction chemotherapy regimen in oral and oropharyngeal squamous cell cancer, in which pCR rate was 31.5% (17/54) [6]. Since the pCR rate of induction chemotherapy was relatively low, major pathological response (MPR) or FPR, which were both defined as $\leq 10\%$ of residual viable tumor after induction chemotherapy, were used as surrogate criteria of pathological response evaluation and endpoints for survival [3]. MPR evaluation requires reviewing multiple

sections, which should be made at least one slide per centimeter of greatest tumor diameter. Though the pathological analysis procedure was not performed according to the criteria of MPR evaluation, the pathological response in our study was assessed by examination of at least 20 slides of each radical tumor resection specimen, the pathological evaluation was reliable. No significant difference in baseline characteristics, including the T stage or TNM stage, was observed between patients with and without FPR, suggesting that FPR could be considered as a prognostic predictor for induction chemotherapy in OSCC.

Therefore, increasing the FPR rate of OSCC patients receiving induction treatment is crucial. On one hand, it is meaningful to find biomarkers that could be used to select OSCC patients who might be sensitive to induction chemotherapy, on the other hand, better induction chemotherapy regimens would be also beneficial. Attempts to intensify TPF with cetuximab to increase efficacy on HNSCC demonstrated no significant effectiveness but was rather toxic [7]. Since immunotherapy demonstrated efficacy in HNSCC and some other cancers, such as esophageal squamous cell carcinoma and triple-negative breast cancer, with excellent tolerability, it has been currently tested in combination with chemotherapy [8, 9]. In the CheckRad-CD8 trial, induction treatment with cisplatin/docetaxel and durvalumab/tremelimumab achieved a high biopsy-proven pCR rate (48%), providing a promising type of regimen for induction chemotherapy [10].

In conclusion, TPF induction chemotherapy failed to improve the survival of unselected patients with locally advanced OSCC. However, patients achieving FPR from TPF induction chemotherapy had significantly improved OS, DFS, LRFS, DMFS, and DSS, compared to patients who failed to achieve FPR or did not receive induction chemotherapy. Our results suggest that FPR could be used as a surrogate endpoint for induction therapy trials in OSCC. It is crucial to identify patients who could obtain a satisfactory pathological response from TPF induction chemotherapy. Meanwhile, induction chemotherapy regimens with higher pathological response are urgently needed.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial was approved by the Institutional Ethics Committee, Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine. Each patient signed informed consent before participating in this trial.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

DISCLOSURE

There is no disclosure.

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AUTHOR'S CONTRIBUTIONS

CPZ, LPZ, ZYZ designed the study. WTJ, YL, LZW, JL, GXR, JS, WYT, YJH, TJ, WJY, Jun L, YH, YAW conducted the study and collected the data. WTJ, YL, LZW analyzed the data and interpreted the results. WTJ, YL wrote the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.