Comparison of Concurrent Chemoradiotherapy or Radiotherapy alone after Induction Chemotherapy for Hypopharyngeal Cancer

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Abstract

Objectives Our study aimed to compare the efficacy and toxicity of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) or radiotherapy (RT) alone in patients with locally advanced hypopharyngeal squamous cell carcinoma (HPSCC). Design: Cohort Retrospective study Settings: Data of HPSCC patients collected from 2008 to 2020 Participants: 83 HPSCC patients Main outcomes measures: 83 patients with HPSCC in our center, who received IC followed by either CCRT or RT alone according to multidisciplinary team (MDT) discussion, were eligible for analysis. Among these patients, 52 patients underwent CCRT and 31 received RT alone after IC and we compared the two groups. Then we further compared the IC + CCRT and IC+RT groups in IC responders showing complete response (CR) and partial response (PR). Survival, toxicities clinical efficacy and outcomes were analyzed. Results For IC responders, IC+CCRT compared to IC+RT improved the locoregional relapse-free survival (LRPFS) (median: 39.3 vs.15.13 months; P=0.033), distant metastasis-free survival (DMFS) (median: 21.37 vs. 13.6 months; P=0.044), PFS (median: 27.87 vs.11.37 months; P=0.048) and the overall survival (OS) (median: 39.33 vs. 18.03 months, P=0.027). A multivariate analysis confirmed IC+CCRT was a positive prognostic factor for LRPFS and OS. However, for either all patients or IC non-responders, IC+CCRT did not improve the survival compared to IC+RT. Regarding acute toxicity, toxicities except [?]2 leucopenia were not statistically different between the two groups. Conclusion In the IC responders, CCRT may possess the survival benefit compared to RT alone in patients with HPSCC. Moreover, the toxicities of two groups were comparable during the therapy. Keywords hypopharyngeal carcinoma, induction chemotherapy, chemoradiotherapy, radiotherapy, survival

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Running title: "IC+CCRT" or "IC+RT" for hypopharyngeal Cancer

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Disclosure Statement

The authors declare no conflicts of interest

Author contributions

All the authorship contributed to the work and approved the final version of

the manuscript.

Conception and study design, development of methodology: WWH and SY;

Data collection, formal analysis, writing – original draft, review & editing: WM and ZD;

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Data available upon reasonable request from the corresponding authors

Abstract

Objectives

Our study aimed to compare the efficacy and toxicity of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) or radiotherapy (RT) alone in patients with locally advanced hypopharyngeal squamous cell carcinoma (HPSCC).

Design: Cohort Retrospective study

Settings: Data of HPSCC patients collected from 2008 to 2020

Participants: 83 HPSCC patients

Main outcomes measures:

83 patients with HPSCC in our center, who received IC followed by either CCRT or RT alone according to multidisciplinary team (MDT) discussion, were eligible for analysis. Among these patients, 52 patients underwent CCRT and 31 received RT alone after IC and we compared the two groups. Then we further compared the IC + CCRT and IC+RT groups in IC responders showing complete response (CR) and partial response (PR). Survival, toxicities clinical efficacy and outcomes were analyzed.

Results

For IC responders, IC+CCRT compared to IC+RT improved the locoregional relapse-free survival (LRPFS) (median: 39.3 vs.15.13 months;P= 0.033), distant metastasis-free survival (DMFS) (median: 21.37 vs. 13.6 months; P= 0.044), PFS (median: 27.87 vs.11.37 months;P =0.048) and the overall survival (OS) (median: 39.33 vs. 18.03 months, P =0.027). A multivariate analysis confirmed IC+CCRT was a positive prognostic

factor for LRPFS and OS. However, for either all patients or IC non-responders, IC+CCRT did not improve the survival compared to IC+RT. Regarding acute toxicity, toxicities except [?]2 leucopenia were not statistically different between the two groups.

Conclusion

In the IC responders, CCRT may possess the survival benefit compared to RT alone in patients with HPSCC. Moreover, the toxicities of two groups were comparable during the therapy.

Keywords

hypopharyngeal carcinoma, induction chemotherapy, chemoradiotherapy,

radiotherapy, survival

Key points

1: Surgery for hypopharyngeal cancers remained unsatisfactory especially for the patients with advanced stages.

2: Non-surgical approaches such as IC, CCRT and radiotherapy were considered more and more for advanced HPSCC patients, however, we have not reached an agreement for the non-surgical treatments due to the limited clinical studies.

3: IC followed by CCRT was beneficial for survival of HPSCC patients when compared to IC followed by RT alone in IC responders but not in all the patients and IC non-responders.

4: IC followed by CCRT was the independent protective factor for LRPFS and OS.

5: IC followed by CCRT did not bring about the severer acute toxicities for HPSCC patients when compared to IC followed by RT alone.

Introduction

Hypopharyngeal squamous cell carcinoma (HPSCC) is a rare malignancy, merely accounting for about 3%-5% of head and neck cancers.[1, 2] Due to the distinct local anatomical characteristics and enriched lymphatic and vascular networks, HPSCCs are commonly diagnosed at an advanced stage.[3, 4] According to previous reports, the 5-year overall survival (OS) was only 30%-35%. [3, 5]

Although advances in oncology treatment for head and neck cancers have been proposed, treatment outcomes in patients with HPSCC are still unsatisfactory, and only minimal improvement in survival has been achieved over the years. In a retrospective study of 6647 HPSCC patients, the average 5-year OS increased marginally from 37.5% (1973-1989) to 41.3% (1990-2003).[6]

Therefore, an ideal therapeutic strategy for HPSCC remains a challenge that requires multidisciplinary teams (MDT) to collaborate for the best outcomes. Before the 1990s, whereas total laryngectomy was the main treatment for locally advanced HPSCCs, its negative impact on the patients was unignorable which vastly affect the patient's quality of life.[7] Considering the disadvantages of surgical method, non-surgical strategies were prioritized from two of the representative random clinical trials in laryngeal cancer[8] and hypopharyngeal cancer,[9]which demonstrated that induction chemotherapy (IC) plus radiotherapy (RT) outperformed laryngectomy in terms of both laryngeal preservation and non-jeopardization of survival.

A variety of studies were recently conducted for the optimization of non-surgical therapy; however, the trials were conducted in patients with head and neck cancers,[10-12] leading to an insufficient evidence regarding non-surgical therapy for HPSCCs. And there were still lacking the unified standard non-surgical therapies. Further, according to the National Comprehensive Cancer Network (NCCN) guideline,[13] locally advanced HPSCCs are often managed by IC followed by (chemo)radiotherapy as a non-surgical strategy. However,

the overall benefits of IC followed by concurrent chemotherapy (CCRT) (IC+CCRT) and IC followed by RT alone (IC+RT) were not clear; thus, our study was performed to assess the efficacy and toxicity associated with the two approaches.

Materials and methods

Patients and patient workup

This study was derived from 269 patients who were diagnosed with HPSCC at our center between August 2008 and October 2020. 83 patients who received IC followed by CCRT (n=52) or IC followed by RT alone (n=31) were included after exclusions (Supplementary Figure 1). All patients underwent disease staging using the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.[13]

The study protocol was approved by the ethics committee of the Beijing Cancer Hospital and Institute, Peking University School of Oncology (approval number: 2019YJZ76). All patients were provided written informed consent for the treatment.

Treatment

MDT collaboration was operated in our hospital, which aimed to provide the patients with the most suitable approach. Based upon the advanced stage of 83 patients, who appeared high risk of distant metastasis for the patients with HPSCC, our center tended to treat the locally advanced patients with IC first, and then decided which approach would be conducted.

IC according to MDT included taxnanes plus platinum with fluorouracil (TPF, n=54), taxanes with platinum (TP, n=15) and fluorouracil with platinum (PF, n=14), all the modalities were administered every 3 weeks.

After IC, CCRT (n=52) or RT alone (n=31) was performed according to the tolerance of patients and MDT discussion. Concurrent chemotherapy was administered every 3 weeks combined with cisplatin or nedaplatin (100 mg/m^2 or 80 mg/m^2, dependent on the patients' health condition).

All patients underwent computed tomography (CT)-based RT planning with intensity-modulated radiotherapy (IMRT). Gross tumor volume (GTV) was divided into primary (GTVp) and nodal (GTVnd). Clinical target volume (CTV) included GTVp and additional margins according to the location of the lesion and the presence of adjacent invasions. The CTV of the nodal regions was determined based on the levels of the metastatic lymph nodes. The prescription doses of 95% planning GTV (PGTV) and 95% planning CTV (PTV) were 70 Gy and 60 Gy, respectively, in 33 fractions (once daily, 5 days per week).

Treatment-related toxicities were analyzed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).

Definition of clinical efficacy

The sites of treatment failure were assessed based on the patients' medical records. The Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) was used to define response assessment after IC treatment. In our study, both laryngoscopy and CT or MRI scans of the neck were used to evaluate the efficacy of the primary tumor. The patients were grouped based on the overall assessment of IC efficacy: IC responders were defined as the patients with CR or PR, and IC non-responders were defined as the patients with stable disease (SD) or progressive disease (PD). OS, progression-free survival (PFS), distant metastasis-free survival (DMFS) and locoregional progression-free survival (LRPFS) were conducted to depict the survival of the patients, all of which were calculated from the start of therapy and adopted the varied endpoints.

Follow-up

Follow-up visits included evaluation of symptoms, physical examination, blood tests, cancer biomarkers, thyroid function tests, endoscopy, CT or magnetic resonance imaging (MRI) scans of the neck and thorax,

and ultrasonography of the cervical and abdominal regions. These were accomplished 1 month after the completion of RT, every 3 months in the first 2 years, every 6 months between years 3 and 5, and once a year thereafter.

Statistical analyses

Categorical variables were compared using $\chi 2$ tests or Fisher's exact tests. OS, PFS, DMFS and LRPFS were compared using the Kaplan–Meier method with log-rank test. Cox regression analysis was used to estimate hazard ratios (HR) and 95% confidence interval (CI). Variables with aP <0.10 in univariate analyses were included in a multivariate analysis. Variables analyzed in our univariate analysis study included gender (male vs female), age (<56y vs [?]56), treatment modality (IC+CCRT vs IC+RT), smoking (no vs yes), alcohol consumption (no vs yes), T stage (T1-2 vs T3-4), N stage (N0-2 vs N3), overall stage (III/IVA vs IVB), modality of IC (PF/TP vs TPF), cycle of IC treatment ([?]2 vs >2), and toxicities during treatment (<3 grade vs [?]3 grade).

The SPSS Statistics for Windows, version 24.0 (IBM, Chicago, IL), was used for statistical analysis. All statistical tests were based on a two-sided significance level, and P -values of <0.05, were considered indicative of a statistically significant finding.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. For the entire cohort, 78 were male and 5 were female and the median age was 56 (39-72). The primary sites were in the pyriform sinus in 70 patients, pharyngeal wall in 8, and post-cricoid pharynx in five. Two patients were in stage III, 40 patients were in stage IVA, and 41 patients were in stage IVB. Both median of cycles of IC and CCRT were 2 (1-4). The detailed tumor-node-metastasis (TNM) stages before IC were shown in Table S1. Besides, the baseline characteristics of the two subgroups of IC responders and non-responders were shown in Table S2.

Tumor responses to induction chemotherapy

As shown in Table 2, the responders with overall CR and PR were 57.8% (n=48) and non-responders with SD or PD were 42.2% (n=35). The reasons why non-responders received RT or CCRT rather than surgery were individual inclination to non-surgical strategies (n=15, 42.9%), inoperable tumors (n=2, 5.7%), and low surgical curability (n=18, 51.4%). Conclusively, based upon the inaccessibility to surgery and overall evaluation from the MDT, the IC non-responders underwent the CCRT or RT instead of surgery.

Clinical efficacy and Patterns of failure

At the end of treatment, the clinical efficacy of all the patients and IC responders was shown in Table S3. Besides, differed patterns of failure as the endpoints for LRPFS, DMFS and PFS of all the patients and IC responders were shown in Table S4.

Survival

The median follow-up time for all patients was 30.2 months. For all patients, IC+CCRT group showed no prolonged LRPFS (median: 21 vs.15.3 months, P =0.825; Figure 1A), DMFS (median: 21.37 vs. 13.6 months,P =0.839; Figure 1B), PFS (median: 20.17 vs.11.38 months,P =0.906; Figure 1C) and OS (median: 27.1 vs.18.03 months,P =0.846; Figure 1D) compared to IC+RT alone group. However, for IC responders, IC+CCRT comparing to IC+RT alone significantly prolonged the LRPFS (median: 39.3 vs. 15.13 months, P =0.033; Figure 2A), DMFS (median: 27.87 vs.13.6 months, P =0.044; Figure 2B), PFS (median:27.87 vs.11.37 months, P =0.048; Figure 2C) and OS (median:39.33 vs.18.03 months, P =0.027; Figure 2D). Notably, IC+CCRT failed to benefit for survival compared to IC+RT alone in IC non-responders (Supplementary Figure 2A-D).

Further, multivariate analysis for the IC responders showed that IC+CCRT was benefit factor for LRPFS (HR: 0.391, 95% CI: 0.16-0.957,P =0.04), and OS (HR:0.361, 95% CI:0.141-0.922, P =0.033) (see Table 3).

Acute Toxicities

The most common [?]3 grade toxicities were neutropenia (n=21, 25.3%) and leukopenia (n=14, 16.9%) during IC and mucositis (n=26, 31.3%), radiation dermatitis (n=5, 6.0%), leukopenia (n=5, 6.0%), and neutropenia (n=5, 6.0%) during (chemo)radiotherapy. The toxicities during therapies between the IC+CCRT and IC+RT groups were shown in Table 4. Except that the [?]2 grade leukopenia during IC was lower in the IC+CCRT group than in the IC+RT group (23.1% vs. 67.7%, P <0.001), other toxicities had no differences between IC+CCRT and IC+RT.

Laryngeal outcomes at the last follow-up

In the last follow-up, 38 patients remained alive, of whom 13 experienced grade 1 voice alteration and one experienced grade 2 voice alteration; moreover, 12 patients had grade 1 dysphagia and 2 had grade 2 dysphagia. Only one patient each underwent percutaneous gastrectomy and tracheotomy due to severe pharyngeal dysfunction after 4 months of RT.

Discussion

IC is an organ-preserving therapeutic approach for treating locally advanced hypopharyngeal cancers. Our study represents a retrospective single-center analysis of assessment of CCRT or RT after IC and demonstrated that IC+CCRT could improve LRPFS and OS in the group of IC responders. To the best of our knowledge, this study is the first to compare the efficacy and toxicity of CCRT and RT following IC in patients with HPSCC.

In our study, the CR rate for primary sites and survival were lower than their counterparts reported in the European Organization for Research and Treatment of Cancer (EORTC) 24891.[9] Several factors could cause this difference. Firstly, it may be due to the majority of patients in our study belonging to T3-4 (79.5%) and stage IV (97.6%), according to the EORTC 24891, patients with T2 stage HPSCC (18/22, 82%) were found to be more accessible to CR (P =0.002) than patients with T3 (34/71, 48%) and T4 stages (0/4). Secondly, this is likely due to the different measurements involved in the efficiency assessment in our study. Both laryngoscopy and neck CT scan were involved in our study; however, a neck CT scan was not mandatory in EORTC 24891. Lastly, our study included patients with PR and non-responders besides CR patients.

Except for EORTC 24891, the OS in our study resembled that of a previous study.[14] Some other RCTs showed higher CR rate and OS in patients with a higher proportion of T2-3 and N0-1 compared to our study.[10, 15] Moreover, laryngeal cancer was included in the research cohorts in some of those RCTs.

In our study, higher LRPFS and OS occurred in the IC responders who received CCRT than in those who received RT alone. Based on our findings, an effort to improve responsiveness to IC becomes the key point. Admittedly, compared to CCRT alone, IC+CCRT has not yet been validated to be advantageous for the survival of patients with locally advanced head and neck cancers in phase III clinical trials.[16, 17] But it has been demonstrated that IC could reduce the risk of distant metastasis [18]. Besides, IC was considered advantageous for survival when performing in the patients with heavily affected primary sites or advanced nodal involvement (cN2c-N3) [19]. Based on the high proportion of N2c (n=27, 32.5%) and N3b (n=37,44.6%) in our study, which had the high risk of distant metastasis, IC was chosen as the prior treatment.

A recent phase II/III trial indicated that patients who underwent IC followed by CCRT had better survival outcomes than those who underwent CCRT alone for head and neck cancer (median survival: 54.7 vs. 31.7%,P =0.03).[20] Furthermore, a retrospective study aiming at laryngeal and hypopharyngeal cancers demonstrated a similar conclusion that IC+CCRT resulted in a longer median OS (64.7 vs. 21%,P =0.003) than CCRT alone for hypopharyngeal cancers, but no survival benefit was found in laryngeal cancers.[21] IC

plays a crucial role in laryngeal preservation(LP)-oriented combination therapy for HPSCCs. This is also supported by the NCCN guideline in which IC was recommended as a strategy for LP.[13]

As concluded in our study, the effect of CCRT after IC correlated with IC responses. The French Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) 2000-01 trial, which included 213 patients with laryngeal or hypopharyngeal cancer, demonstrated the superiority of the TPF regimen over PF in terms of ORR (80.0% vs. 59.2%, P =0.002) and LP rate (70.3% vs. 57.5%, P =0.03).[15] With the exception of ORR and LP rates, another two RCT trials showed that TPF markedly improved PFS and OS in locally advanced head and neck cancers.[22, 23] Conceivably, aiming at the effectiveness of CCRT combined with IC, TPF should be prioritized for IC treatment rather than PF.

Regarding IC non-responders, more careful therapeutic considerations are required. Nowadays, with the advancement of individualized cancer care with increasing precision and more implications, and with the incorporation of multicenter novel therapies, such as immunotherapy, the access to an ideal trade-off status between the expected clinical outcomes and a less-affected quality of life potentially comes into real practice.[24]

Regarding the exclusiveness of this series, owing to the prevailing characteristics of many studies involving multiple sites of head and neck cancer, HPSCC comprises only a minority of the ensemble population due to its low prevalence. In some researchers about head and neck subsites, hypopharyngeal cancer generally merged with laryngeal cancer. Therefore, critical featured information for HPSCC treatment would be incomprehensive, leading to a shortage of definite conclusions. Exploration of optimal treatment for HPSCCs to some degree counts on the personal experiences of clinicians and the results, including the confounding factors that may render them less convincing. Herein, our study focused only on patients with HPSCC and offered exclusive information regarding their treatment, which will be helpful in clinical practice. The overall efficacy assessment for IC was used to group the patients in our study rather than only aiming for the primary sites, which brought about more reasonable evaluations for the comparison of CCRT and RT alone.

Regarding limitations of our study, due to the small sample size and retrospective nature of our study, the comparison of CCRT and RT alone according to IC responses requires further investigation with larger cohorts or prospective trials. Moreover, as no patients achieved CR after IC treatment, more studies are required to investigate the necessity of CCRT.

Conclusion

In our study, a comparison of IC+CCRT and IC+RT responses showed that IC+CCRT improved the survival of IC responders and brought about manageable toxicities in all patients. Based on limited numbers of reports about HPSCC, our study has conveyed the detailed clinical data about HPSCC and indicate that IC+CCRT would be a promising non-surgical strategy in patients with locally advanced HPSCC.

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Figure legends

Figure 1 Kaplan-Meier estimation of LRPFS (A), DMFS (B), PFS (C), OS (D) cures for 83 patients stratified as IC+CCRT and IC+RT groups.

Abbreviations: LRPFS=locoregional progression-free survival; DMFS=distant metastasis-free survival; PFS=progress-free survival; OS=overall survival; IC=induction chemotherapy; CCRT=concurrent chemoradiotherapy; RT=radiotherapy.

Figure 2 Kaplan-Meier estimation of LRPFS (A), DMFS (B), PFS (C), OS (D) cures for 48 patients with responders to IC stratified as IC+CCRT and IC+RT groups.

Abbreviations: LRPFS=locoregional progression-free survival; DMFS= distant metastasis-free survival; PFS=progress-free survival; OS=overall survival; IC=induction chemotherapy; CCRT=concurrent chemoradiotherapy; RT=radiotherapy.

Supplementary Figure 1 Flow diagram of our study.

Abbreviations: IC=induction chemotherapy; RT=radiotherapy;

CCRT=concurrent chemoradiotherapy.

Supplementary Figure 2 Kaplan-Meier estimation of LRPFS (A), DMFS (B), PFS (C), OS (D) cures for 35 patients with non-responders to IC stratified as IC+CCRT and IC+RT groups.

Abbreviations: LRPFS=locoregional progression-free survival; DMFS=distant metastasis-free survival; PFS=progress-free survival; OS=overall survival; IC=induction chemotherapy; CCRT=concurrent chemoradiotherapy; RT=radiotherapy.

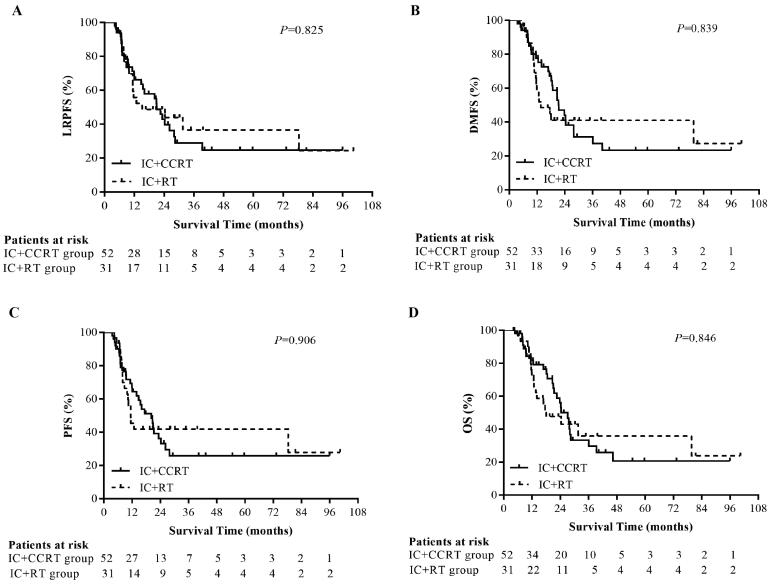

FIGURE 1: Kaplan-Meier estimation of LRPFS (A), DMFS (B), PFS (C), OS (D) cures for 83 patients stratified as IC+CCRT and IC+RT groups. Abbreviations: LRPFS=locoregional progression-free survival; DMFS=distant metastasis-free survival; PFS=progress-free survival; OS=overall survival; IC=induction chemotherapy; CCRT=concurrent chemoradiotherapy; RT=radiotherapy.

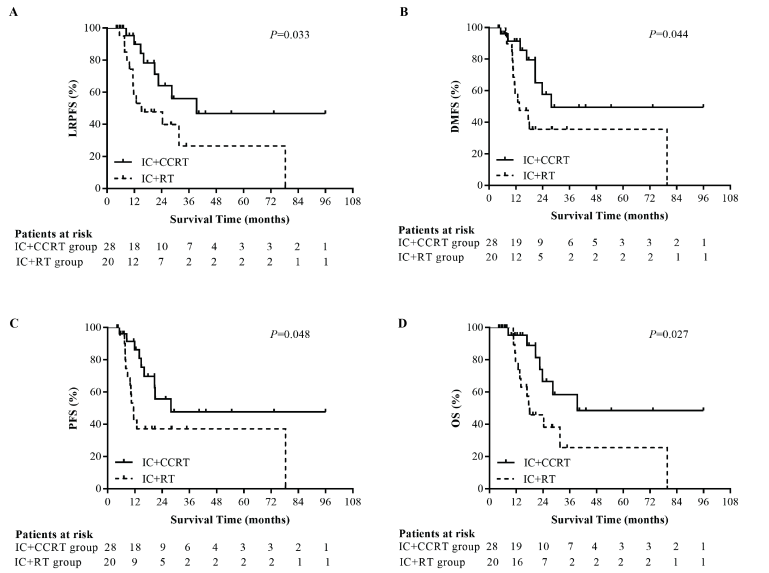

FIGURE 2 Kaplan-Meier estimation of LRPFS (A), DMFS (B), PFS (C), OS (D) cures for 48 patients with responders to IC stratified as IC+CCRT and IC+RT groups. Abbreviations: LRPFS=locoregional progression-free survival; DMFS= distant metastasis-free survival; PFS=progress-free survival; OS=overall survival; IC=induction chemotherapy; CCRT=concurrent chemoradiotherapy; RT=radiotherapy.

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