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Research article

The clinical outcomes of induction chemotherapy followed by radiotherapy vs. chemoradiotherapy in locally advanced hypopharyngeal squamous cell carcinoma: A retrospective study

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ABSTRACT

Background: Stage III and IVA–B hypopharyngeal carcinoma presents a substantial risk of recurrence and metastasis. The treatment strategy remains uncertain. The objective of this observational study was to compare the outcomes of induction chemotherapy followed by radiotherapy (ICRT) and induction chemotherapy followed by chemoradiotherapy (ICCRT) in the treatment of locally advanced hypopharyngeal squamous cell carcinoma.

Methods: 58 patients with stage III and IVA–B hypopharyngeal squamous cell carcinoma treated with ICRT (n = 26) or ICCRT (n = 32) were enrolled in the study. Baseline variables and toxicity rates were compared by Chi-squared test. Survival curves were constructed by the Kaplan-Meier method and compared by log-rank test. Multivariate Cox proportional hazard analysis was performed to evaluate the potential survival effects.

Results: There were no significant differences in gender, age, smoking, drinking, T category, N category, overall stage, induction chemotherapy schemes and cycles between the two groups. The median follow-up time was 36.3 months (range, 2.3–97.5 months). The 2-year recurrence-free survival (RFS), locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and the 1-year, 2-year overall survival (OS) expressed no significant differences between the two groups. Furthermore, induction chemotherapy regimen of TPF achieved better OS than TP or PF (hazard ratio [HR] 0.395, 95 % confidence interval [CI] 0.178–0.879; $P = 0.023$), OS of patients in N2-3 category was worse than N0-1 (HR 2.594, 95 % CI 1.230–5.471; $P = 0.012$). In addition, the grade 3–4 therapy-associated toxicities during radiotherapy were higher in the chemoradiotherapy group than in radiotherapy alone group ($P = 0.020$).

Conclusion: Following induction chemotherapy in patients with stage III/IVA-B hypopharyngeal squamous cell carcinoma, the concurrent chemoradiotherapy regimen provided similar survival rates with radiotherapy alone. Meanwhile, the incidence of treatment-related side effects during radiotherapy after induction chemotherapy were lower than that during chemoradiotherapy.

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1. Introduction

Head and neck cancer is the sixth most common cancer in the world, with approximately 890,000 new cases and 450,000 deaths each year, accounting for a significant proportion of global mortality [1–3]. Hypopharyngeal cancer is an important part of this, with more than 84,000 new cases and 38,000 deaths in 2020 [4]. Squamous cell carcinoma (SCC) of the hypopharynx, accounting for about 3 % of head and neck cancer, is a highly aggressive pathological type with hidden lesions, which is usually diagnosed at an advanced stage and has poor survival rates with 5-year overall survival (OS) of about 30–35 % [5,6].

According to the National Comprehensive Cancer Network (NCCN) guidelines [7], for early-stage (stage I or II) patients, conservative surgery and radiotherapy (RT) are the primary treatment options with similar local control. Furthermore, RT is also an important therapeutic approach for local advanced hypopharyngeal cancer (stage III or IV), which can be combined with surgery and chemotherapy. Many studies indicated that, comparing to surgery, definitive radiation therapy can effectively preserve the larynx in a large proportion of patients with advanced hypopharyngeal cancer without compromising OS [8–12]. In the early 1990s, several randomized trials about larynx-preservation were conducted using induction chemotherapy as initial treatment [8,13,14]. Long-term follow-up confirmed that induction chemotherapy (TPF) combined with docetaxel, cisplatin and 5-fluorouracil (5-FU) increased larynx preservation and laryngeal dysfunction-free survival. TPF has been demonstrated to be superior to the platinum/5-FU regimen and has been used as the standard induction chemotherapy regimen [15,16]. Thus, induction chemotherapy of TPF regimen followed by radiation therapy is widely used in clinical practice for local advanced hypopharyngeal carcinoma patients with greater local control and improved OS than RT alone [16]. A long-term follow-up study of phase III clinical trial evaluating the efficacy of concurrent chemoradiotherapy (CRT) following induction chemotherapy versus CRT alone in patients with unresectable locally advanced head and neck SCC showed no significant difference in OS between the two groups. But patients with larynx–hypopharynx primary tumors who received induction chemotherapy followed by CRT had longer progression-free survival (PFS) than those who received CRT alone [17]. However, it still remains controversial whether induction chemotherapy followed by CRT (ICCRT) can confer further survival benefits compared to induction chemotherapy followed by RT (ICRT). Although a limited number of studies have reported ICCRT treatment outcomes for head and neck SCC, they have included a mixture of early and advanced cases and have not compared the

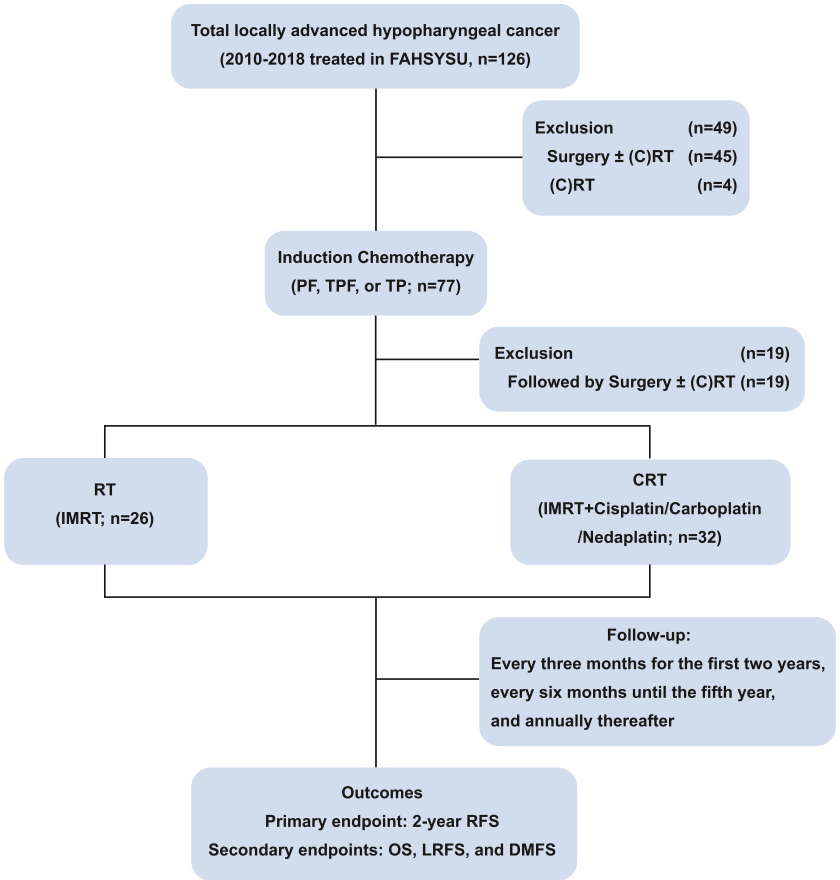

Fig. 1. Flowchart illustrating research. **Abbreviations:** RT = radiotherapy; CRT = chemoradiotherapy; PF = cisplatin+ 5-fluorouracil; TPF = docetaxel + cisplatin+ 5-fluorouracil; TP = docetaxel + cisplatin; IMRT = intensity-modulated radiation therapy; RFS = recurrence-free survival; OS = overall survival; LRFS = locoregional recurrence-free survival; DMFS = distant metastasis-free survival.

efficacy of ICRT and ICCRT [18–20]. Thus, the purpose of this study was to evaluate the efficacy of ICRT and ICCRT in the treatment of locally advanced stage III and IVA-B hypopharyngeal SCC, with a view to finding another treatment mode that can improve patient outcomes.

2. Materials and methods

2.1. Patients

From January 2010 to January 2018, a total of 126 patients diagnosed with locally advanced (stage III/IVA-B) hypopharyngeal squamous cell carcinoma in First Affiliated Hospital of Sun Yat-Sen University (FAHSYSU) were enrolled for preliminary screening, as illustrated in Fig. 1. Patients who did not receive induction chemotherapy (n = 49) or underwent surgery after induction chemotherapy (n = 19) were excluded. The selection criteria were as follows: (1) Patients with stage III or IVA–B (TNM stageT1-2N1-3M0/T3-4aN0-3M0) hypopharyngeal SCC confirmed by histopathology, including the piriform fossa, postcricoid area, and posterior pharyngeal wall according to the American Joint Committee on Cancer (AJCC) eighth edition [21]; (2) Age from 18 to 70 years old; (3) Patients with partial response after induction chemotherapy; (4) Good performance status (KPS ≥70); (5) Normal renal, cardiac and liver function; (6) Complete follow-up data. The exclusion criteria were as follows: (1) History of other cancers within the last five years; (2) Patients who have previously undergone RT or surgery (except biopsy); (3) Patients receiving palliative therapy; (4) Any severe coexisting disease. Consequently, data of 58 patients with stage III or IVA–B hypopharyngeal carcinoma who received ICRT (n = 26) or ICCRT (n = 32) were retrospectively collected and analyzed.

2.2. Diagnosis and treatments

Detailed pretreatment evaluation of the extent of the primary tumor and lymphatic metastasis included endoscopy, ultrasound with or without ultrasound-guided fine-needle aspiration biopsy, computed tomography (CT), Magnetic Resonance Imaging (MRI), and positron emission tomography (PET)-CT. Patients were restaged according to the TNM staging system in the AJCC eighth edition [21].

The therapeutic regimen was strictly in accordance with the NCCN guidelines [22]. The treatment modality was formulated by the multi-disciplinary team based on the tumor size and site, the possibility of radical resection, the general performance status of the patient, and the preferences of each patient. The patients with stage III and IVA–B of locally advanced hypopharyngeal SCC received the following treatment: neoadjuvant chemotherapy followed by radical RT with or without concurrent chemotherapy. Induction chemotherapy consisted of cisplatin with 5-fluorouracil or taxane, or a combination of all three, administered every three weeks for two or three cycles. Namely, induction chemotherapy regimens were as follows: (1) PF: 5-fluorouracil (FU) 600 mg/m^2/day with continuous infusion for 120 h on days 1–5, cisplatin 60 mg/m^2 on day 1; (2) TPF: docetaxel 60 mg/m^2 on day 1 with 5-FU 600 mg/m^2/day on days 1–5 for 120 h and cisplatin 60 mg/m^2 on day 1; (3) TP: docetaxel 75 mg/m^2 on day 1 and cisplatin 75 mg/m^2 on day 1. Patients received two or three cycles of one of these treatment protocols. Imaging was followed up after completion of induction chemotherapy, and the efficacy was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [23]. After induction chemotherapy, final RT or CRT was given depending on the choice of the doctors and the patients.

For radiation therapy, all patients received intensity-modulated radiation therapy (IMRT). Target delineation was performed using Radiation Therapy Oncology Group guidelines. The planning target volume (PTV) was defined as the primary tumor (PTVp) and positive lymph node (PTVn), the high-risk planning target volume (PTV-HR) was defined as the PTVp with an appropriate margin, and the low-risk PTV (PTV-LR) was defined as PTV-HR with an appropriate margin plus selective lymph node region. The treatment included conventional fractionation RT with a total dose of 68–70 Gy for PTVp, 62–68 Gy for PTVn, 60–62 Gy for PTV-HR, and 50–54 Gy for PTV-LR. In the ICCRT group, concurrent chemotherapy regimens concluded (1) Cisplatin: cisplatin 100 mg/m^2 on day 1; (2) Carboplatin: Carboplatin 100 mg/m^2 on day 1; (3) Nedaplatin: Nedaplatin 100 mg/m^2 on day 1; three weeks as one cycle. Patients received one or two cycles of one of these treatment regimens during RT.

During the course of treatment, full dose chemotherapy was given for three weeks according to hematologic parameters (white blood cell [WBC] count >3500/ml and platelet count >100,000/ml). If the WBC count before therapy was between 2500/ml and 3499/ml or the platelet count was 75,000 to 99,000/ml, the dose of both agents needed to be reduced by 50 %. Chemotherapy was suspended either the WBC count was below 2500/ml or the platelet count was below 75,000/ml.

2.3. Follow-up

We obtained a complete medical history of all patients who underwent physical examinations, blood tests, head and neck CT or MRI, chest CT, whole-body ^{18}F-fluorodeoxyglucose PET-CT and endoscopy prior to treatment [24]. Hematological and biochemical profiles were examined once a week during induction chemotherapy and RT. After the treatment ended, patients were followed up regularly every three months for the first two years, then every six months until the fifth year, and annually thereafter. Follow-up evaluations during each visit contained physical examination, hematological and biochemical profiles, CT or MRI scan, chest radiography, abdominal ultrasonography, whole body bone scan, and PET-CT. The therapeutic effect was assessed using RECIST 1.1 criteria [23]. Treatment-related toxicities were evaluated based on the Com Terminology Criteria for Adverse Events (CTCAE) version 5.0. Whenever possible, local or distant recurrences were identified by fine needle aspiration or biopsy. For the sites where histological examination were unavailable, clinical diagnosis would be acceptable if there were classic changes (with or without clinical symptoms) on at least two imaging methods, including CT, MRI, chest radiography, abdominal ultrasonography, bone scan, and

^{18}F-fluorodeoxyglucose PET-CT. However, if imaging results were also ambiguous, subsequent follow-up (e.g., disease progression) would be needed to confirm the diagnosis. Each treatment endpoint was assessed by the attending physician. Where possible, remedial treatments, including symptomatic treatment, chemotherapy, surgery, or re-RT, were provided in accordance with standard procedures for documented cases of recurrent or persistent disease.

2.4. Outcomes

The primary endpoint for this study was 2-year recurrence-free survival (RFS), which measured from the date of initial treatment to locoregional/distant recurrence or death or the time of the last follow-up, whichever occurred first. Secondary endpoints included OS, locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and toxicity. OS was defined as the time interval between the diagnosis of hypopharyngeal cancer and death or last follow-up. LRFS was defined as the time from the start of treatment until locoregional recurrence. DMFS was defined as the time from the start of treatment to the discovery of distant metastasis. The research process was outlined in Fig. 1.

2.5. Statistical analysis

All statistical analyses were performed by IBM SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Survival outcomes were assessed using the Kaplan–Meier method and compared with the log-rank test. The correlation between concurrent chemotherapy and treatment outcomes were estimated by univariate and multivariate Cox regression models and the Chi-squared test. The factors with *P*-value $\leq$0.05 in the univariate analysis were enrolled into the multivariate Cox regression model. All tests were bilateral, and *P*-value $<$0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 58 eligible patients composed of 53 men and five women were included. Of these, 26 patients were treated with ICRT and 32 received ICCRT. The demographic data were shown in Table 1. The mean age in the ICRT group was 54.8 years, compared with 57.8 years in the ICCRT group ($P = 0.121$). Clinical features, including smoking ($P = 0.199$), drinking ($P = 0.672$), T category ($P = 0.557$), N category ($P = 0.336$), overall stage of cancer ($P = 0.597$), induction chemotherapy schemes ($P = 0.736$), induction chemotherapy

Table 1
Patient and tumour characteristics.

Variable	Total (n = 58)	ICRT (n = 26)	ICCRT (n = 32)	*P*
Gender (n [%])	58	26	32	0.243
Male	53 [91.4]	25 [96.2]	28 [87.5]	
Female	5 [8.6]	1 [3.8]	4 [12.5]	
Age (years)	56.5 ± 7.5	54.8 ± 7.1	57.8 ± 7.6	0.121
Smoker (n [%])				0.199
Yes	42 [72.4]	21 [80.8]	21 [65.6]	
No	16 [27.6]	5 [19.2]	11 [34.4]	
Drinker (n [%])				0.672
Yes	33 [56.9]	14 [53.8]	19 [59.4]	
No	25 [43.1]	12 [46.2]	13 [40.6]	
T category (n [%])				0.557
T2	15 [25.9]	6 [23.1]	9 [28.1]	
T3	29 [50.0]	15 [57.7]	14 [43.8]	
T4	14 [24.1]	5 [19.2]	9 [28.1]	
N category (n [%])				0.336
N0	13 [22.4]	6 [23.1]	7 [21.9]	
N1	11 [19.0]	7 [26.9]	4 [12.5]	
N2	3 [58.6]	13 [50.0]	21 [65.6]	
Stage AJCC 8th (n [%])				0.597
III	18 [31.0]	9 [34.6]	9 [28.1]	
IVAB	40 [69.0]	17 [65.4]	23 [71.9]	
IC Schemes (n [%])				0.736
TPF	46 [79.3]	20 [76.2]	26 [81.3]	
TP	3 [5.2]	1 [3.8]	2 [6.2]	
PF	9 [15.5]	5 [19.2]	4 [12.5]	
IC Cycles	3 (IQR 3-3)	3 (IQR 3-3)	3 (IQR 2–3)	0.824
PTVp radiotherapy dose (Gy)	68.10 (66.00–70.00)	68.05 (64.67–69.52)	68.10 (66.00–70.00)	0.680

Abbreviations: ICRT = induction chemotherapy followed by radiotherapy; ICCRT = induction chemotherapy followed by chemoradiotherapy; T = tumor; N = node; IC = induction chemotherapy; TPF = docetaxel + cisplatin+ 5-fluorouracil; TP = docetaxel + cisplatin; PF = cisplatin+ 5-fluorouracil; PTVp = planning target volume of primary tumor; IQR = inter-quantile range.

cycles ($P = 0.824$), and RT dose ($P = 0.680$) were balanced between the two treatment groups. In the ICRT group, 20 (76.2 %) patients received TPF induction chemotherapy, five (19.2 %) patients received PF and the other one (3.8 %) received TP. While in the ICCRT group, 26 (81.3 %) patients were treated with TPF regimen, four (12.5 %) with PF and the other two (6.2 %) with TP. The median induction chemotherapy cycles of two groups were three (inter-quantile range [IQR] 3–3). The median PTVp RT dose in the ICRT

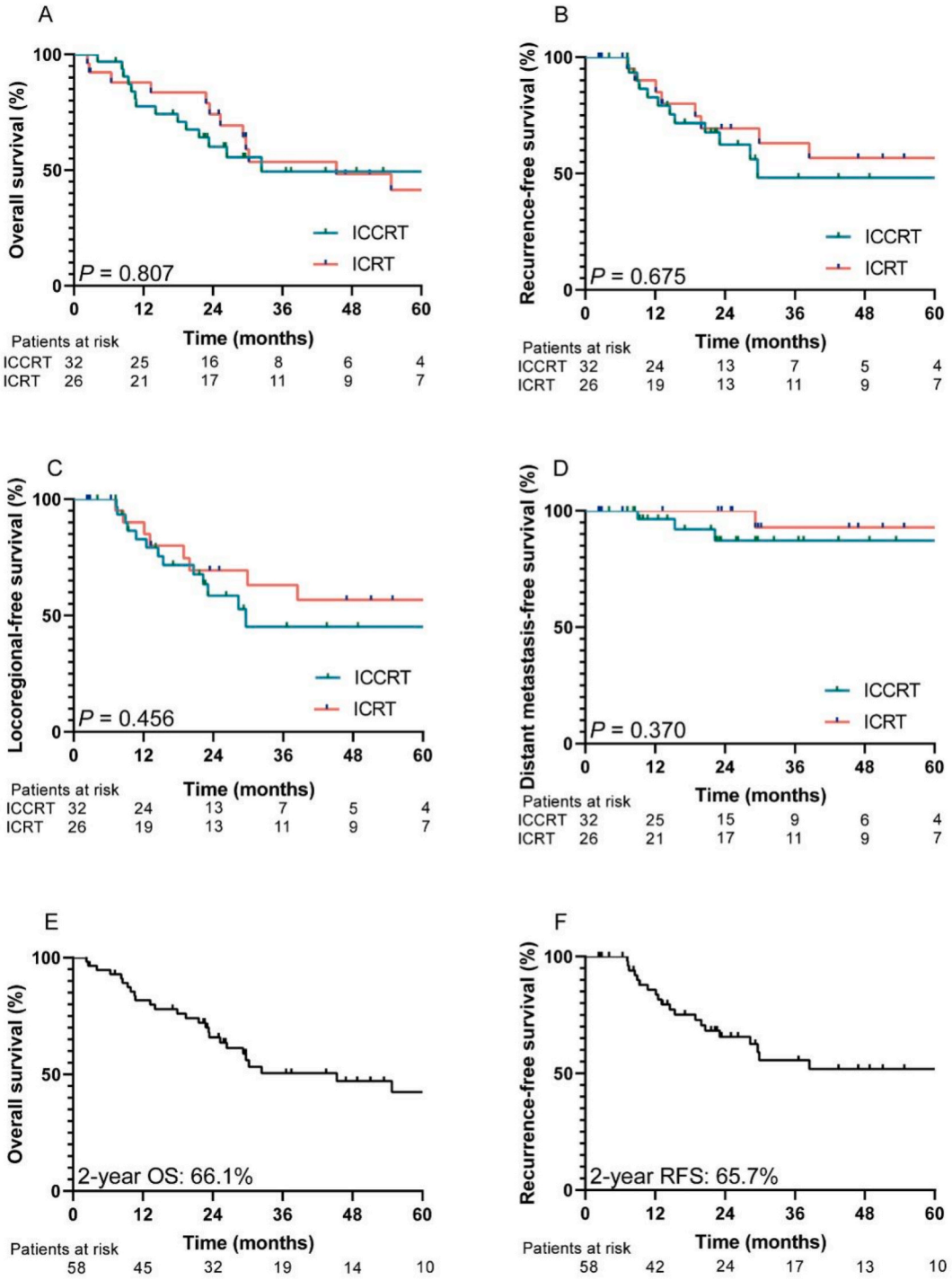

Fig. 2. Survival curves are shown for the ICRT and ICCRT groups. **(A)** OS; **(B)** RFS; **(C)** LRFS; **(D)** DMFS. The 2-year OS **(E)** and 2-year RFS **(F)** for all the 58 patients. **Abbreviations:** ICRT = induction chemotherapy followed by radiotherapy; ICCRT = induction chemotherapy followed by chemoradiotherapy; OS = overall survival; RFS = recurrence-free survival; LRFS = locoregional recurrence-free survival; DMFS = distant metastasis-free survival.

group was 68.05 Gy (IQR 64.67 Gy–69.52 Gy), whereas the corresponding figure for the ICCRT group was 68.10 Gy (IQR 66.00 Gy–70.00 Gy). The dose and duration of RT were similar between two groups ($P = 0.680$). In the ICCRT group, of the 32 patients who received platinum-based drugs as concurrent chemotherapy, 24 (75.0 %) patients completed two cycles of concurrent chemotherapy successfully. The remaining patients were treated with one cycle because of acute hematologic toxicities.

3.2. Survival outcomes

As of the last follow-up on December 24, 2020, the median follow-up time was 29.7 months (range, 2.3–97.5 months) for the ICRT group and 36.7 months (range, 4.1–90.8 months) for the ICCRT group. During follow-up, 14 patients in the ICRT group and 19 patients in the ICCRT group died, they all died of tumor-related causes. The incidence of the first failure event occurring at locoregional or distant sites were 34.6 % (n = 9) and 3.8 % (n = 1) in the ICCRT arm, and 43.8 % (n = 14) and 6.3 % (n = 2) in the ICRT arm, respectively. Salvage surgery for residual or relapsed disease was performed in three ICRT patients and two ICCRT patients ($P = 0.292$). As shown in Fig. 2A–D, the OS, RFS, LRFS, and DMFS expressed no significant differences between the two groups ($P > 0.05$). The cumulative OS of the ICRT group were 87.9 % at 1 year and 74.7 % at 2 years, the ICCRT group were 77.5 % and 61.4 %, respectively ($P = 0.601$). The 2-year RFS were 70.0 % for the ICRT group and 59.9 % for the ICCRT group, respectively ($P = 0.647$). For patients with locally advanced hypopharyngeal cancer, the 2-year LRFS after ICRT and ICCRT were 70.0 % and 56.1 %, respectively ($P = 0.539$), and the 2-year DMFS were 100 % and 92.0 %, respectively ($P = 0.685$). For the patients received TPF induction chemotherapy, the 2-year OS in the ICRT group was 78.0 %, the ICCRT group was 65.4 %, respectively ($P = 0.687$). The 2-year RFS were 73.3 % for the ICRT group and 58.0 % for the ICCRT group, respectively ($P = 0.544$). For the patients who completed 2-cycle concurrent chemotherapy, the cumulative 2-year OS and RFS were 68.2 % and 66.7 %, respectively. There were no significant differences between the two groups in 2-year OS ($P = 0.885$) and RFS ($P = 0.784$). The 2-year OS and RFS for all the 58 patients were 66.1 % and 65.7 %, respectively (Fig. 2E and F).

3.3. Univariate and multivariate analyses

Univariate and multivariate Cox proportional hazard analyses were performed to identify the potential risk factors for RFS, LRFS, DMFS, and OS of all patients, including age, gender, smoking, drinking, tumor stage, induction chemotherapy schemes, induction chemotherapy cycles and concurrent chemotherapy. As presented in Table 2, multivariate analysis showed that induction chemotherapy scheme of TPF achieved better OS than TP or PF (hazard ratio [HR] 0.395, 95 % confidence interval [CI] 0.178–0.879; $P = 0.023$), N2-3 stage achieved worse OS than N0-1 (HR 2.594, 95 % CI 1.230–5.471; $P = 0.012$). There were no significant correlations between the tested factors and RFS, LRFS, and DMFS. By univariate analysis, there were no significant correlations between concurrent chemotherapy and RFS (HR 0.940, 95 % CI 0.367–2.403; $P = 0.896$), LRFS (HR 1.010, 95 % CI 0.400–2.545; $P = 0.984$), DMFS (HR 38.689, 95 % CI 0.000–8426768.676; $P = 0.560$), and OS (HR 0.917, 95 % CI 0.430–1.958; $P = 0.823$).

3.4. Treatment related toxicities

Adverse events during RT in the ICRT and ICCRT groups included neutropenia, anemia, stomatitis, and dermatitis. There were no

Table 2
Cox's proportional hazards regression model of OS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Gender				
Male vs. Female	0.213 (0.029–1.564)	0.128		
Age				
>56.5 vs. ≤ 56.5	0.745 (0.375–1.479)	0.400		
Smoker				
Yes vs. No	1.690 (0.733–3.897)	0.218		
Drinker				
Yes vs. No	1.648 (0.807–3.364)	0.170		
T category				
T3–4 vs. T1–2	1.578 (0.750–3.322)	0.230		
N category				
N2–3 vs. N0–1	2.365 (1.136–4.922)	0.021	2.594 (1.230–5.471)	0.012
Overall stage (8th edition)				
IV vs. III	2.243 (0.901–4.274)	0.073		
IC Schemes				
TPF vs. Others	0.455 (0.209–0.991)	0.048	0.395 (0.178–0.879)	0.023
IC Cycles				
>3 vs. ≤ 3	1.126 (0.705–1.800)	0.619		
CCRT				
Yes vs. No	0.917 (0.430–1.958)	0.823		

Abbreviations: HR = hazard ratio; CI = confidence interval; IC = induction chemotherapy; TPF = docetaxel + cisplatin+ 5-fluorouracil.

differences in the incidence of hematological adverse events during RT between the two treatment groups, except that the incidence of grade 3–4 neutropenia was higher in the ICCRT group (25.0 %) than in the ICRT group (3.8 %) ($P = 0.027$). Three patients suffered grade 3–4 liver damage during RT in ICCRT group. Among the 32 patients in the ICCRT group, eight (25 %) patients only accepted one cycle chemotherapy because of acute toxicity in hematologic toxicities. In terms of non-hematological toxicity, the incidence of grade 3–4 nausea or vomiting was higher in the ICCRT group than in the ICRT group (21.9 % versus 3.8 %, $P = 0.048$). These results were shown in Table 3.

4. Discussion

For local advanced hypopharyngeal SCC patients, RT following induction chemotherapy has been widely used in clinic work and can effectively provide larynx preservation. However, there still lacks an optimal strategy orchestrating chemotherapy and RT after induction chemotherapy currently. Especially, clinical patients may suffer from more toxicities during IMRT with concurrent chemotherapy following induction chemotherapy, which leads to the suspend of RT. Moreover, discontinuing or extending treatment may reduce the effectiveness of RT as we all know [25]. In a subgroup of a previous retrospective study, the 2-year disease-free survival (DFS) and OS of ICCRT were about 60 % and 55 %, respectively, which were similar to this present study. However, it enrolled some patients with early stage and didn't compare the clinical outcomes between the ICCRT group and ICRT group [6]. Therefore, our study compared the efficacy of ICRT and ICCRT, and the results showed that it improved neither RFS, LRFS, DMFS nor OS in local advanced hypopharyngeal SCC patients when concurrent chemotherapy was added to IMRT after induction chemotherapy, suggesting that ICRT may be sufficient to treat these patients.

According to the previous trials, which were different from our results, the survival benefit of simultaneous CRT exceeds individual RT in locoregionally advanced nasopharyngeal carcinoma (NPC), regardless of the addition of adjuvant chemotherapy, which improved the 5-year OS from about 58 % in RT to about 73 % in CRT ($P < 0.05$) [26–28]. Besides, a meta-analysis showed that the addition of concurrent chemotherapy (using cisplatin, mitomycin C, or F) to hyper-fractionated RT improved OS (HR 0.77, 95 % CI 0.66–0.89; $P < 0.001$), and PFS (HR 0.74, 95 % CI 0.63–0.87; $P < 0.001$) in the definitive treatment of advanced locally advanced head and neck SCC (oral cavity, oropharynx, hypopharynx, and larynx) [29]. However, these previous studies were from NPC or mixed head and neck cancer trials. Furthermore, the patients in previous trails were treated in 1994–2002, received 2D RT. This study was the first in the literature to compare the efficacy of ICRT and ICCRT groups in the treatment of locally advanced hypopharyngeal SCC and showed that the addition of concurrent chemotherapy to IMRT after induction chemotherapy did not improve OS, RFS, LRFS, and DMFS. The reasons of varying results may be as follows: considering the admission time and highly aggressive characteristics, the median follow-up time was only 36.3 months (range, 2.3–97.5 months) in our study, however, the primary endpoint, 2-year RFS, was similar in two groups, that may be worth noticing. Besides, considering the complexity of tumor site, their surrounding structures, and the frequent comorbidities, the CRT-related toxicity was more frequent and serious in hypopharyngeal SCC than in NPC, leading to the halt of RT, especially in the patients who following induction chemotherapy.

Moreover, over the past 15 years, IMRT, as an advanced form of conformal RT that can target tumors more precisely while reducing dose to normal tissues, has displaced other radiation technologies in the treatment of most head and neck cancers, which can improve regional control compared to traditional 2D radiation therapy [30–32]. Many retrospective studies had suggested that IMRT alone may be sufficient to treat stage II NPC [33]. Besides, a previous retrospective study reported that adding chemotherapy to RT after induction chemotherapy appeared to provide similar survival benefit as RT alone in patients with locally advanced NPC [29,34]. Therefore, concurrent CRT compared to RT alone after induction chemotherapy may not improve patient prognosis. Beyond that, because of the small sample size and short follow-up time in our study, the long-term survival effect cannot be accurately reflected until now. Further follow-up and even basic experimental studies of hypopharyngeal SCC are needed.

Additionally, regarding the type of drugs to be combined concomitantly with RT, in comparison to the importance of dose intensity,

Table 3
Frequency of treatment-related adverse events during radiotherapy.

Adverse event (%)	ICRT (n = 26)		ICCRT (n = 32)		*P* for events Grades 1–2	*P* for events Grades 3–4
	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4		
Hematological						
Neutropenia	61.5	3.8	59.4	25.0	0.867	0.027
Thrombocytopenia	50.0	3.8	53.1	9.4	0.813	0.409
Anemia	73.1	15.4	71.9	9.4	0.919	0.485
Liver dysfunction	19.2	0.0	15.6	9.3	0.718	0.254
Non-hematological						
Stomatitis	76.9	19.2	71.8	25.0	0.662	0.600
Dermatitis	65.4	15.4	71.8	18.8	0.595	0.736
Xerostomia	57.7	7.7	56.3	3.1	0.912	0.435
Anorexia	53.8	11.5	53.1	6.25	0.956	0.475
Nausea or vomiting	57.7	3.8	62.5	21.9	0.710	0.048
Dysphagia	34.6	3.8	37.5	9.3	0.820	0.820

Abbreviations: ICRT = induction chemotherapy followed by radiotherapy; ICCRT = induction chemotherapy followed by chemoradiotherapy.

differences in radiosensitivity and adverse events among diverse dosing regimens may be neglected, where the accumulation of 200 mg/m^2 cisplatin may be the threshold for optimal efficacy during RT [35]. However, many patients received platinum-based drugs in our study could not complete the concurrent chemotherapy plan due to the intolerance of these adverse effects of concurrent chemoradiation. On the other hand, TPF induction chemotherapy has been added to RT or surgery to try to decrease the likelihood of emergence of distant metastasis, improve the opportunity to receive radical surgery, reduce local toxicity of RT, and support organ preservation via reducing tumor volume [15,36].

Observing the adverse events of the two treatments, the incidence of grade 3–4 neutropenia was much higher in ICCRT-treated patients (25 %) than in ICRT (3.8 %), suggesting increased toxicity ($P = 0.027$). Several studies have reported that concurrent CRT increased the risk of treatment-related complications. Arlene et al. did a phase III trial comparing cisplatin chemoradiation (n = 172) with RT alone (n = 173) in patients with locally advanced laryngeal cancer, it reported that patients receiving RT and cisplatin simultaneously not only had chemotherapy-associated toxic effects (e.g., neutropenia and nausea or vomiting), but also an increased incidence of severe radiation-related mucosal, pharyngeal, and esophageal reactions [13].

In addition, recent researches have indicated that the PD-1/PD-L1 axis was routinely altered in a significant proportion of patients with head and neck SCC, so that the PD-1/PD-L1 axis can be selectively blocked to treat tumors, especially in locally advanced and metastatic patients, which can be combined with other therapies for systemic treatment [16,37,38]. A retrospective study compared the efficacy of neoadjuvant chemotherapy alone versus neoadjuvant chemotherapy combined with PD-1 inhibitors (neoadjuvant chemoimmunotherapy) in patients with hypopharyngeal SCC. The results indicated that neoadjuvant chemoimmunotherapy showed strong antitumor activity, with the overall response rate reached 81.0 % and the complete and partial response rates of 14.9 % and 65.9 %, respectively. Furthermore, neoadjuvant chemoimmunotherapy exhibited better PFS and OS [39]. Due to the investigation period of our study from 2010 to 2018, there were few patients receiving immunotherapy, so we did not conduct further research. However, other studies have shown that immunotherapy can be used as the alternative option for patients with locally advanced hypopharyngeal cancer, more data will be updated in the future to explore this point.

While, there are some limitations in our study. This study was retrospective and had a small sample size, which was likely leading to a bias in selecting patients who received either ICRT or ICCRT. Besides, the cases were enrolled from a single center, thus, the results of this study may not be representative of all hypopharyngeal carcinoma patients. In addition, the type of drugs to be combined concomitantly with RT was inconsistent in our study, including cisplatin, carboplatin, or nedaplatin, which might influence the survival outcomes. Based on that, a randomized prospective study which comparing the two strategies is on-going.

5. Conclusions

In this retrospective study, we compared the efficacy of ICRT and ICCRT for stage III/IVA-B hypopharyngeal SCC, there were no significant differences of survival between the two groups. And induction chemotherapy scheme of TPF achieved better OS than TP or PF (HR 0.395, 95 % CI 0.178–0.879; $P = 0.023$), N2-3 stage achieved worse OS than N0-1 (HR 2.594, 95 % CI 1.230–5.471; $P = 0.012$) by multivariate Cox proportional hazards regression analysis. Meanwhile, the incidence of treatment-related toxic reactions during ICRT expressed lower than that during ICCRT. Thus, RT without concurrent chemotherapy after induction chemotherapy may be sufficient for treating locally advanced hypopharyngeal SCC when the adverse events are acceptable. These results provide the basis for further research into the use of other therapeutic modalities such as immunotherapy in combination with CRT in the challenging clinical settings.

Ethics statement

As a retrospective observational study, this study was conducted using medical records obtained in previous clinical diagnosis and treatment, without prior collection of specimens or prospective follow-up, and had no risk to the subjects. The Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University has applied for waiver from signing informed consent and approved it. The study was reviewed and approved by the IEC for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University ([2024]442).

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Ke Jiang: Writing – original draft, Validation, Methodology, Formal analysis. **Meiyan Zhu:** Writing – original draft, Visualization, Methodology, Formal analysis. **Shasha He:** Investigation, Data curation. **Chengtao Wang:** Validation, Resources. **Yan Wang:** Validation, Resources. **Yufeng Ren:** Investigation, Data curation. **Zijun Xiang:** Investigation. **Yong Chen:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Yong Chen reports financial support was provided by National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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