Investigational New Drugs (2019) 37:352–359
https://doi.org/10.1007/s10637-018-00720-0

PHASE II STUDIES

IMRT combined with S-1 concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: a prospective phase II study

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Received: 30 November 2018 / Accepted: 25 December 2018 / Published online: 8 January 2019

Summary

Purpose The current standard treatment for locally advanced nasopharyngeal carcinoma (LANPC) is intensity-modulated radiation therapy (IMRT) plus cisplatin concurrent chemoradiotherapy (CCRT). However, this regimen has well-known hematological and gastrointestinal toxicities. Many studies have reported that S-1 was effective in the treatment of multiple solid cancers with mild toxicities. However, knowledge regarding IMRT plus S-1 CCRT in LANPC is lacking. Therefore, we conducted this prospective phase II trial to evaluate the efficacy and safety of this regimen in LANPC. *Patients and Methods* Eligible patients with histologically confirmed LANPC were enrolled in this study. IMRT was given in 30–32 fractions five times per week. Concurrently, S-1 was administrated twice per day orally based on the body surface area (BSA < 1.25 m^2, 30 mg; BSA: 1.25–1.5 m^2, 40 mg; BSA > 1.5 m^2, 50 mg). The primary endpoints were progression-free survival (PFS) and adverse events. *Results* From August 1, 2013, to December 15, 2017, 131 patients were enrolled in this study. The distribution of disease stages among the patients was as follows: 21 patients were in stage II (16.0%), 42 patients were in stage III (32.0%), and 68 patients were in stage IV (52.0%). After CCRT, the 3-year PFS, overall survival (OS), local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) rates were 87.4%, 95.7%, 94.7%, and 91.5%, respectively. The severity of most toxicities was mild. Approximately two-thirds of patients had no hematological toxicity. Grade 2 hematological toxicities included leukopenia (11.5%), anemia (1.5%), and thrombocytopenia (0.8%). Grade 3 hematological toxicities were rarely observed. *Conclusion* The results demonstrated that IMRT plus S-1 CCRT was effective with mild toxicity for patients with LANPC.

Keywords Nasopharyngeal carcinoma · S-1 · IMRT · Hematological toxicities

Introduction

Nasopharyngeal carcinoma (NPC) is highly endemic in China and Southeast Asia [1–3]. According to the GLOBOCAN 2012, the estimated global incidence and mortality of NPC in 2012 were 86,691 and 50,831, respectively [4]. Due to the special anatomical location of the nasopharynx, most NPC patients present with an advanced stage at first diagnosis [5]. Moreover, the prognosis of locally advanced nasopharyngeal carcinoma (LANPC) is relatively dismal because of its high metastasis rate [1, 2, 6, 7].

Intensity-modulated radiation therapy (IMRT) combined with cisplatin concurrent chemoradiotherapy (CCRT) is recommended as the standard treatment for patients with LANPC by the National Comprehensive Cancer Network Guidelines (NCCN 2017 Version) [6]. Many studies have demonstrated that cisplatin-based CCRT could improve the efficacy than

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10637-018-00720-0) contains supplementary material, which is available to authorized users.

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radiotherapy alone, but the relatively severe toxicities, including hematological toxicity, gastrointestinal toxicity, renal toxicity, hepatic toxicity, and ototoxicity, cannot be ignored [5, 6, 8–10]. Anne's randomized phase III study showed that cisplatin-based CCRT could improve 5-year progression-free survival compared with radiotherapy alone ($p = 0.035$), while the incidence of acute toxicity increased by 30% ($p < 0.001$) [10]. Some retrospective and prospective studies have suggested that cisplatin-based CCRT had more toxic effects than cetuximab/nimotuzumab-based CCRT [5] and nedaplatin-based CCRT [6] with comparable efficacy. It was reported that cisplatin-associated toxicities were related to an approximately 1% increased mortality rate [8, 11]. Moreover, many NPC patients discontinued cisplatin-based CCRT treatment because they could not tolerant the cisplatin-associated toxicities. The compliance rates of cisplatin-based CCRT were 65% in Tang's study [6] and only 52% in the Hong Kong NPC- 9901 trial [12]. Therefore, alternative chemoradiotherapy regimens are urgently needed to minimize toxicities without affecting the efficacy for patients with LANPC.

S-1 is an oral 5-fluorouracil (5-FU) prodrug that was designed to improve antitumor activity and reduce the toxicities of 5-FU [13–15]. S-1 consists of tegafur (a prodrug of 5-FU), gimeracil and potassium oxonate [13–15]. Gimeracil can inhibit the degradation of 5-FU, maintaining high 5-FU concentrations in tumor tissues [14, 15]. Moreover, it was reported that gimeracil could enhance the efficacy of radiotherapy through the suppression of homologous recombination-mediated DNA repair pathways [16]. After oral administration, potassium oxonate is distributed throughout the gastrointestinal mucosa and reduces the gastrointestinal toxicities induced by the phosphorylation of 5-FU [14, 15]. Many studies in the past few decades have demonstrated that S-1 monotherapy was effective and safe in head and neck cancer [17–19], gastric cancer [20–25], and lung cancer [26, 27]. Recently, S-1 combined with IMRT CCRT has also achieved promising efficacy with mild toxicities in elderly patients with gastric cancer [28] and non-small cell lung cancer [26]. In addition, Wen's prospective phase II study demonstrated that CCRT of 2D-RT (Two Dimension Radiotherapy) combined with S-1 was effective and safe [11]. However, the clinical role of IMRT combined with S-1 CCRT in LANPC is still uncertain. Therefore, we conducted this prospective phase II study to evaluate the efficacy and safety of IMRT combined with S-1 CCRT for patients with LANPC.

Patients and methods

Patient eligibility

This study was a prospective phase II trial that evaluated the efficacy and safety of IMRT combined with S-1 CCRT for patients with LANPC. The eligibility criteria included histologically confirmed LANPC according to the American Joint Committee on Cancer (AJCC) Staging System (the eighth edition); the Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; at least one measurable lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST, criteria 1.1); normal complete blood count (white blood cell counts $\geq 4 \times 10^{12}$/L, hemoglobin level ≥ 100 g/L and platelet counts $\geq 100 \times 10^{12}$/L); normal hepatic function (total bilirubin level ≤ 1.5 mg/dl, alanine aminotransferase and aspartate aminotransferase levels ≤ 1.5 times the upper limit of normal); and normal renal function (creatinine ≤ 1.5 times the upper limit of normal). Prior induction chemotherapy with platinum was allowed.

Exclusion criteria included previous radiotherapy; a history of any other type of malignancy; pregnancy or lactation; allergy to S-1; failure of liver, renal, cardiac or lung function; uncontrolled infection; systemic or distant metastasis; severe gastrointestinal diseases; and mental disorders affecting the patient's judgement regarding their participation in the trial.

Study design

This study was an open-label, single-arm phase II study. The primary endpoints were progression-free survival (PFS) and adverse events. The secondary endpoints were overall survival (OS) and objective response rate (ORR). The study protocol was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center. This study is registered with ClinicalTrials.gov with the number NCT 03668366 and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Pretreatment evaluation

A histological diagnosis of the primary disease was required for every patient. Pretreatment evaluations included a complete history and physical examination emphasizing the head and neck area, nasopharyngoscopy, biopsy, complete blood counts, liver function tests, and renal function tests. Unless clinically contraindicated, all patients performed enhanced magnetic resonance imaging (MRI) scans of the nasopharynx and neck, chest computed tomography (CT) scans, abdomen sonography, and bone scans. Positron emission computed tomography (PET-CT) and plasma Epstein-Barr virus DNA load were measured if possible.

Treatment

All patients in this study received IMRT. Gross tumor volume (GTV) included all primary tumor lesions and the enlarged lymph nodes observed in clinical and imaging examinations. CTV1 was defined as a high-risk clinical target volume which

included the bilateral parapharyngeal space, the pterygopalatine fossa, the posterior section of the nasal cavity, the maxillary sinus (limited to 5 mm anterior to the posterior nasal aperture and maxillary mucosa), the posterior ethmoid sinus, the skull base, the anterior third of the clivus, the inferior sphenoid sinus and the cavernous sinus. CTV1 also included the bilateral retropharyngeal nodal regions from the base of the skull to the cranial edge of the hyoid bone, the bilateral space of the retro-styloid process, and the bilateral upper neck lymph node drainage area above the cricoid cartilage. Low-risk clinical target volume (CTV2) included the lower neck lymphatic drainage area. The IMRT dose prescription was as follows: 66–70.4 Gy to GTV, 57–60.8 Gy to CTV1, and 54–56 Gy to CTV2, given in 30–32 fractions. Radiation was delivered once per day in 5 fractions per week.

During the IMRT, S-1 was administrated orally according to the body surface area (BSA < 1.25 m^2, 30 mg; BSA: 1.25–1.5 m^2, 40 mg; BSA > 1.5 m^2, 50 mg) twice per day (Fig. 1). Dose modifications of S-1 were not permitted during the concurrent chemotherapy except for the progression of the disease, toxicities of grade 4 or patient's refusal.

During the administration of S-1, patients were not allowed to take fluorouracil antitumor drugs that had a similar antitumor mechanism to S-1. Moreover, the administration of drugs including warfarin and phenytoin sodium was also forbidden due to the interactions between S-1 and these drugs.

Follow up /statistical considerations

Adverse events (AEs) were evaluated every week during concurrent chemoradiotherapy based on the evaluation criteria of adverse reactions of CTCAE V4.0. Tumor response was assessed four weeks after concurrent chemoradiotherapy was completed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. Radiation-related acute and late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG). Late toxicities were evaluated after three months from the start of radiotherapy.

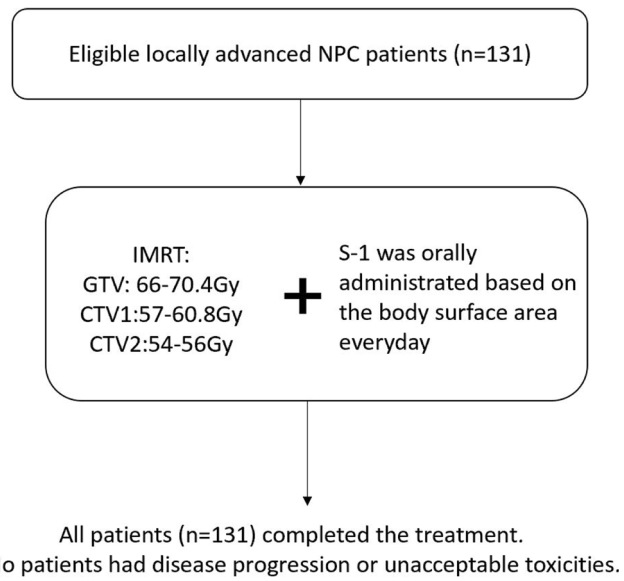

Fig. 1 Patient flowchart

After the completion of the concurrent chemoradiotherapy treatment, all patients were followed up every 3 months during the first years, every 6 months for the following 2–5 years, and annually thereafter. Local recurrences were confirmed by nasopharynx MRI or histological biopsy. Regional recurrences were detected by a clinical examination of the neck and were confirmed by neck MRI or histologically with fine needle aspiration. Distant metastases were detected by imaging examinations including PET-CT, bone emission computed tomography (ECT), chest CT and abdominal sonography or were confirmed by histological confirmation of a biopsy.

The PFS, OS, local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) rates were calculated by the Kaplan–Meier method. PFS was calculated from the date of enrollment to the date of disease progression or the date of death for any cause. OS was calculated from the date of enrollment to the date of death for any cause. LRFS was calculated from the date of enrollment to the date of local recurrence or the date of death for any cause. DMFS was calculated from the date of enrollment to the date of distant metastasis or the date of death for any cause. The data were analyzed using SPSS (SPSS Inc. Chicago, IL, USA) software (version 19.0). Survival curves were performed by GraphPad Prism (version 5.0) using the Kaplan-Meier method with a log-rank test.

Results

Patient characteristics

From August 1, 2013, to December 15, 2017, 131 patients were enrolled in this study at the Shanghai Cancer Center. The characteristics of the patients are summarized in Table 1. The median age of the patients was 53 years (range from 18 to 76), and thirty-three patients (25.2%) were aged over 65 years. The distribution of the disease stages of the patients was as follows: 21 patients were in stage II (16.0%), 42 patients were in stage III (32.0%), and 68 patients were in stage IV (52.0%). Among the patients in this study, 83 patients (63.4%) were male, and 48 patients (36.6%) were female. All patients had at least one measurable lesion and good ECOG PS of 0–1. The pathology of patients was mostly nonkeratinized nasopharyngeal cancer (98.5%). Only two patients had keratinized nasopharyngeal carcinoma (1.5%). Among the 131 NPC patients, 47 patients (35.9%) were treated with prior paclitaxel and cisplatin induction chemotherapy; 55 patients (42.0%) were treated with prior paclitaxel and nedaplatin induction chemotherapy; 7 patients (5.3%) were treated with prior gemcitabine and cisplatin

Table 1 Patient characteristics

Characteristics	Number of patients ($n = 131$)	%
Gender		
Male	83	63.4%
Female	48	36.6%
Age		
≥65	33	25.2%
<65	98	74.8%
Median	53	
Range	18–76	
Pathology		
WHO I	2	1.5%
WHO II-III	129	98.5%
T (AJCC8)		
1	22	16.8%
2	34	26.0%
3	42	32.0%
4	33	25.2%
N(AJCC8)		
0	9	6.9%
1	42	32.0%
2	42	32.0%
3	38	29.1%
TNM(AJCC8)		
II	21	16.0%
III	42	32.0%
IV	68	52.0%
ECOG		
0	13	9.9%
1	118	90.1%
Induction chemotherapy		
Paclitaxel + Cisplatin	47	35.9%
Paclitaxel + Nedaplatin	55	42.0%
Gemcitabine +Cisplatin	7	5.3%
None	22	16.8%
Total	131	100%

ECOG Eastern Cooperative Oncology Group
AJCC American Joint Committee on cancer

induction chemotherapy; and 22 patients (16.8%) did not receive any induction chemotherapy.

Efficacy

IMRT combined with S-1 CCRT was administrated to all 131 patients. As summarized in Table 2, 63 patients achieved the complete response (CR, 48.1%), 65 patients had the partial response (49.6%), and three patients had stable disease (2.3%). The objective response rate (ORR) was 97.7%, and the disease control rate (CR + PR + SD) was 100%.

Table 2 Tumor response of S-1 combined with IMRT in locally advanced nasopharyngeal carcinoma

Tumor response	Number of patients	%
CR	63	48.1%
PR	65	49.6%
SD	3	2.3%
ORR	128	97.7%
DCR	131	100%
Total	131	100%

CR complete response, *PR* partial response, *SD* stable disease, *ORR* objective response rate, *DCR* disease control rate

With a median follow-up period of 24.5 months (range 7–58 months), the 3-year PFS, OS, LRFS and DMFS rates were 87.4%, 95.7%, 94.7% and 91.5%, respectively (Fig. 2). However, the median PFS, OS, LRFS, and DMFS rates had not yet been reached. In addition, there were no significant differences in PFS ($p = 0.0863$), OS ($p = 0.6961$), LRFS ($p = 0.5270$), or DMFS ($p = 0.2566$) between the induction chemotherapy of paclitaxel plus cisplatin (TP) regimen and the paclitaxel plus nedaplatin (TN) regimen (Supplementary Figure).

Adverse events

In this study, no patient received the dose modification of S-1. With no patients discontinuing the treatment of S-1, the compliance rate in our study was 100%. Moreover, most toxicities of IMRT combined with S-1 CCRT were mild. As summarized in Table 3, no grade 4 toxicities or treatment-related deaths were observed. Regarding hematological toxicity, only one patient (0.8%) developed grade 3 leukopenia, and one patient (0.8%) had grade 3 thrombocytopenia. The incidences of mucositis were grade 1 (1.5%), grade 2 (77.1%) and grade 3 (21.4%). The most common nonhematological toxicities were anorexia (55.8%), weight loss (54.2%), nausea (51.9%), vomiting (51.2%), and fatigue (53.4%). Moreover, no renal toxicity, ototoxicity, or hepatic toxicity were observed.

Regarding late toxicities, there were no grade 4 late toxicities and no treatment-related deaths. No temporal lobe necrosis was observed. The most common late toxicities were xerostomia (64.2%) and neck fibrosis (51.9%). The grade 2 toxicity rates of xerostomia, neck fibrosis, dysphagia, trismus, cranial nerve palsy and hearing loss were 11.5%, 3.8%, 0.8%, 0.8%, 0.8% and 0%, respectively.

Discussion

The concurrent chemoradiotherapy of IMRT combined with cisplatin is the standard treatment modality for patients with

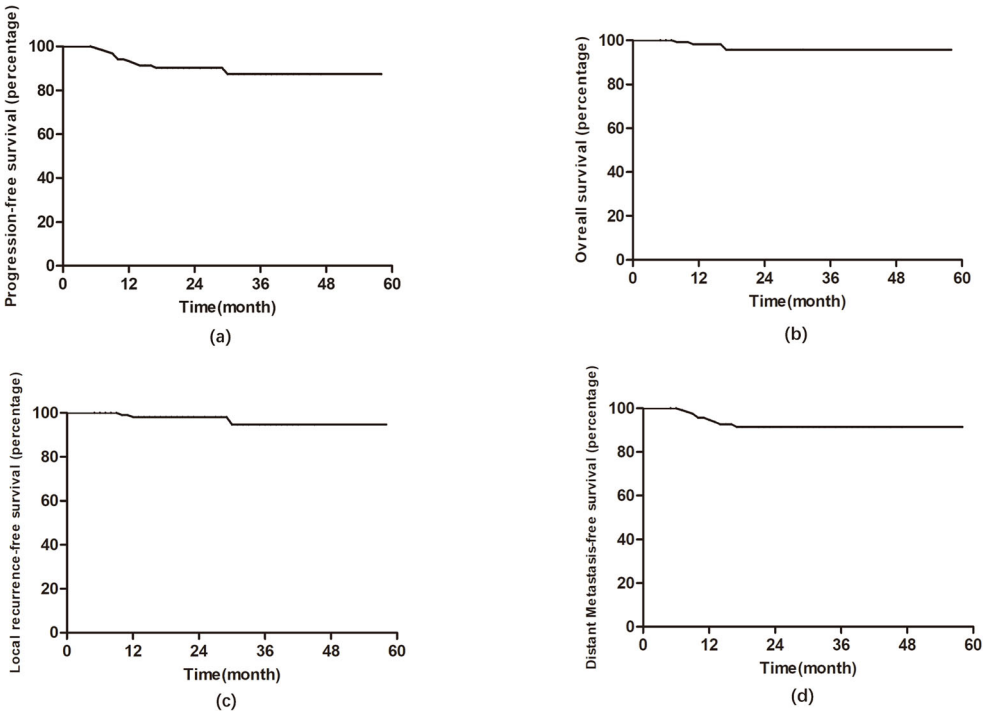

Fig. 2 Kaplan-Meier curves of progression-free survival (**a**), overall survival (**b**), local recurrence-free survival (**c**) and distant metastasis-free survival (**d**) of S-1 combined with IMRT concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma

LANPC [6, 29]. However, many patients suffer from cisplatin-associated toxicities and have relatively poor compliance [6]. To address this issue, a variety of novel chemotherapy regimens have been evaluated for patients with LANPC in recent years. The third generation of platinum, including nedaplatin and lobaplatin, demonstrated comparable efficacy and fewer toxicities than cisplatin in LANPC patients [6, 29]. The overall responses of IMRT plus nedaplatin CCRT and IMRT plus lobaplatin CCRT were 99% and 100%, respectively, in LANPC patients, which were similar to the ORR of 97.7% observed in this study [6, 29]. However, severe hematological toxicities still occurred with platinum-based CCRT, with grade 3 leukopenia (23%), anemia (<1%) and thrombocytopenia (5%) in the nedaplatin group [6] and grade 3 leukopenia (33.9%), anemia (16.9%) and thrombocytopenia (27.1%) in the lobaplatin group [29]. Anti-EGFR monoclonal antibodies cetuximab (CTX) and nimotuzumab (NTZ) combined with IMRT were reported to be effective and safe for LANPC patients, with an OS of 91.7% and a severe hematological rate of 3.4–4.7% [5]. However, a big-data retrospective study [30] showed that CTX/NTZ concurrently with induction chemotherapy might be a more effective strategy than concurrently with IMRT for patients with LANPC. Additionally, anti-EGFR antibodies are much too expensive for most NPC patients in China, which limits the widespread use of CTX/NTZ-based CCRT in LANPC patients.

To our knowledge, this study was the first prospective phase II trial to evaluate the efficacy and safety of IMRT combined with S-1 CCRT in LANPC patients. The 3-year PFS and OS rates in this study were 87.4% and 95.7%, respectively, which was comparable with the PFS rate (83.0%) and OS rate (94.9%) obtained in Ke's prospective study of IMRT plus lobaplatin CCRT [29]. The randomized phase III trial by Tang et al. [6] suggested that nedaplatin plus IMRT was an alternative doublet treatment strategy to standard cisplatin-based CCRT for LANPC. The PFS rates were similar between these two studies [6]. However, the hematological toxicity rates in this study were much lower than those observed in the Tang study of nedaplatin CCRT [6] and in Ke's study of lobaplatin CCRT [29]. Wen's prospective phase II study of 2D-RT combined with S-1 CCRT [11] resulted in a 2-year PFS of 81.3% and an OS of 86.2%, which further confirmed the antitumor activity of S-1 in LANPC patients. The huge survival distinctions of PFS and OS between this study and Wen's study can mainly be attributed to the application of advanced IMRT technology and the higher dose of S-1 administrated in this study. With the wide application of IMRT, the local control and survival outcomes in LANPC have been highly improved compared to the outcomes resulting from 2D-RT and three-dimensional conformal radiotherapy (3D-CRT) [31]. There was no significant difference in progression-free survival (PFS), overall survival (OS), local recurrence-free survival (LRFS) or distant metastasis-free survival (DMFS) in the paclitaxel plus cisplatin induction chemotherapy group compared with the paclitaxel plus nedaplatin group in this study. The multicenter phase II conducted by Tang et al. [32] also showed an insignificant distinction of

Table 3 Treatment adverse events

Adverse events	All patients ($n = 131$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematological toxicities					
Leukopenia	29 (22.1%)	15 (11.5%)	1 (0.8%)	0 (0%)	0 (0%)
Anemia	46 (35.1%)	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia	32 (24.4%)	1 (0.8%)	1 (0.8%)	0 (0%)	0 (0%)
Non-hematological toxicities					
Mucositis	2 (1.5%)	101 (77.1%)	28 (21.4%)	0 (0%)	0 (0%)
Nausea	24 (18.3%)	39 (29.8%)	5 (3.8%)	0 (0%)	0 (0%)
Vomiting	28 (21.4%)	36 (27.5%)	3 (2.3%)	0 (0%)	0 (0%)
Fatigue	27 (20.6%)	36 (27.5%)	7 (5.3%)	0 (0%)	0 (0%)
Anorexia	19 (14.5%)	42 (32.1%)	12 (9.2%)	0 (0%)	0 (0%)
Weight loss	24 (18.3%)	38 (29.0%)	9 (6.9%)	0 (0%)	0 (0%)
Late toxicities					
Xerostomia	69 (52.7%)	15(11.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neck fibrosis	63 (48.1%)	5 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Temporal necrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysphagia	3 (2.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Trismus	4 (3.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cranial nerve palsy	4 (3.1%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hearing loss	3 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

survival outcomes between the paclitaxel plus cisplatin induction chemotherapy group and the paclitaxel plus nedaplatin group, which was similar to the results of this study.

The toxicities of IMRT combined with S-1 CCRT in this study were mild and reversible. Moreover, the administration of S-1 was more convenient than the intravenous infusion and hydration of cisplatin. The hematological toxicities in our study were mild. The patients in this study demonstrated grade 3 leukopenia (0.8%), anemia (0%) and thrombocytopenia (0.8%), while the grade 3 hematological toxicities in the patients in Tang's study were leukopenia (22%), anemia (3%) and thrombocytopenia (1%) in the cisplatin group, and leukopenia (23%), anemia (<1%) and thrombocytopenia (5%) in the nedaplatin group [6]. Although, with mild hematological toxicities, the grade 2 and 3 mucositis in this study were more common compared to the prevalence of mucositis in Tang's study [6], which could be partly explained by two reasons. After radiotherapy, patients had a poor oral health status, and the high serum concentration of 5-FU can exacerbate mucosal inflammation. However, in this study, grade 3 toxicities were easily identified, prevented and managed. Additionally, 25.2% of patients in this study were aged over 65 years. With no patient discontinuing the treatment, the compliance rate was 100% in this study, which was much higher than the cisplatin group in Tang's study (65%) [6] and in the Hong Kong NPC-9901 trial (52%) [12]. In these two studies, the most common reason for discontinuation of chemotherapy was cisplatin-associated treatment toxicities [6, 12]. In addition, outpatients who received IMRT during the night needed to come to the hospital to receive the infusion of cisplatin during the daytime, which is inconvenient and might affect the patient's rest. If patients can take S-1 orally at home during the IMRT course, which is effective with mild toxicities for nasopharyngeal carcinoma, it will be much more convenient for the treatment of outpatients. In summary, S-1 treatment modality was safe and convenient for patients with LANPC, especially for elderly patients and outpatients who received IMRT during the night.

Regarding the late toxicities, the grade 2 toxicities of xerostomia, trismus, and hearing loss in this study were lower than those observed in Wu's study [33]. However, the neck fibrosis, dysphagia and cranial nerve palsy in this study were more common than those in Wu's study [33], which might be partly attributed to the proportion of stage IV patients in this study (52.0%) being higher than that in Wu's study (42.0%), and the radiation doses delivered on CTV1 and CTV2 were higher than those in Wu's study [33].

There were also several limitations in this study. The first one is the lack of plasma quantitative Epstein-Barr virus (EBV) DNA copy information, which was because we did not routinely perform this test in our hospital several years ago. Second, this study has a relatively short follow-up time, but we had already achieved our primary endpoints. A long-term follow-up is needed to assess survival outcomes and late toxicities of this regimen. Furthermore, a multicenter phase III study is currently being undertaken by our group to determine

the efficacy of S-1-based CCRT versus cisplatin-based CCRT in LANPC patients.

In conclusion, IMRT combined with S-1 CCRT demonstrated favorable efficacy and mild toxicity in LANPC patients. In the future, S-1 combined with IMRT concurrent chemoradiotherapy might become a promising treatment for LANPC, especially for elderly nasopharyngeal carcinoma patients and outpatients.

Acknowledgments This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethical Committee of Fudan University Shanghai Cancer Center.

Informed consent Informed consent was obtained from all individual participants included in the study.

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