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Comparative Study between Patients Treated with Conventional Radiotherapy and IMRT with Chemotherapy for Stage III - IVA Nasopharyngeal Carcinoma: A Single Institution Retrospective Report

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Abstract

Introduction: Nasopharyngeal carcinomas are the most radiation-sensitive tumours, and radiotherapy alone provides better local control. **Objectives**: To evaluate the clinical efficacy and acute and late toxicities of two different treatment regimens for locally advanced nasopharyngeal carcinoma. **Methods**: From 2014 to 2017, 150 cases of stage III and 68 cases of stage IVA nasopharyngeal carcinoma were treated. Of these, 137 received conventional radiotherapy plus chemotherapy, and 81 received intensity-modulated radiotherapy plus chemotherapy. Chemotherapy was given either as induction, concurrent or adjuvant therapy. Survival rates were calculated according to Kaplan Meier and compared with the Log-rank test. The RTOG or EORTC criteria were used to assess acute and late toxicities. **Results**: The median follow-up time was 21.5 months, and the 2-year locoregional relapse-free survival, distant metastases-free survival, and overall survival rates in the conventional radiotherapy plus chemotherapy group were 76%, 71% and 77%, respectively; in the intensity-modulated radiotherapy plus chemotherapy group, they were 97%, 84%, and 100%, respectively. The difference in survival between the two groups was significant (χ^2 = 5.06, P = 0.028). The incidence of grade 2 and 3 xerostomia one year after radiotherapy was 45.1% and 30.9% versus 33.3% and 0%. **Conclusion**: Compared with conventional radiotherapy plus chemotherapy, intensity-modulated radiotherapy plus chemotherapy

offers better locoregional relapse-free survival and overall survival in patients with stage III and IVA nasopharyngeal carcinoma, and may significantly reduce the occurrence of radiation-induced xerostomia.

Keywords

Nasopharyngeal Carcinoma, Conventional Radiotherapy, Intensity Modulated Radiotherapy, Chemotherapy, Prognosis

1. Introduction

Nasopharyngeal carcinomas (NPC) are the most radiation-sensitive tumors, and radiotherapy (RT) alone provides better local control. In patients with early-stage (stages I and II), the 10-year disease-free survival, recurrence-free survival, and metastasis-free survival can reach over 95%, 90%, and 94%, respectively [1]. However, treatment outcomes for locally advanced disease are less than satisfactory. Patients with stage III-IVA NPC had the highest incidence of relapse (61.4%) and death rates (43.2%) [2] [3]. From a practical standpoint, the efficient application of RT in this group is limited by the complex anatomy of the head and neck regions. Factors such as: patient age (≥60 years old), hearing loss, xerostomia, eyeball damage, and a decrease in nutritional status have been suggested as common complications after NPC irradiation. The occurrence rate of grade > 2 hearing loss, xerostomia, radiation induce optic nerve neuropathy, radiation induce retinitis, and even a decrease in nutritional status were respectively 46.8%, 84.4%, 12.5%, 21.9% and 67.0% [4] [5] [6] [7]. In this context, toxicity management during treatment becomes even more important than curative treatment. Nevertheless, the recent advances in clinical imaging, treatment planning, and conformity of dose delivering have resulted in better outcomes [8]. Compared with old techniques conventional RT, intensity modulated radiation therapy (IMRT) can deliver more conformal dose to the tumor site, while better spares adjacent critical organs, thereby improving the local control rate of the primary tumor and reducing the overall exposure of organs at risk. The 5-year actuarial local relapse-free survival (LRFS) rate increased from 86.8% to 92.7% and 5-year disease-free survival (DFS) rate increased from 71.4% to 75.9% for the IMRT group, respectively [9]. Furthermore, patients with metastatic NPC have poor prognosis, with median overall survival of 20 months [10]. Regarding the issue of how to control distant metastasis and improve the overall survival rate in patients with locally advanced NPC, several studies have been initiated over many years in China to provide these patients with better control of distant metastases and thus improve overall survival [10]. The present study aimed to evaluate the results of management strategies for stage III - IVA NPC in terms of locoregional relapse-free survival (LRFS), distant metastases-free survival (DMFS), overall survival (OS) rates and late toxicity, and to provide better knowledge that could help tailor the most effective strategies.

2. Material and Methods

2.1. Patients Clinicopathological Characteristics

A total of 308 patients treated for NPC were selected and retrospectively reviewed at The Fourth Affiliated Hospital of Hebei Medical University. Of these, 218 cases of histologically confirmed stage III - IVA NPC between January 2014 and December 2017 were eligible for inclusion. The complete demographic and clinicopathological characteristics of the 218 patients are presented in Table 1.

Table 1. Clinicopathological characteristics of patients with nasopharyngeal carcinoma.

Factors	All	Conventional RT + CT group	IMRT + CT group	χ^2	P
		n (%)	n (%)		
Gender				0.04	0.895
Male	136 (62.4)	72 (52.6)	64 (70.0)		
Female	82 (37.6)	65 (47.4)	17 (30.0)		
Age				3.28	0.149
Median (year)	49 ± 9.3	48 ± 3.8	52.6 ± 8.2		
<50	121 (55.5)	93 (67.9)	28 (34.6)		
≥50	97 (44.5)	44 (32.1)	53 (65.4)		
Histological grade				2.44	0.296
Poorly and moderate differentiated	160 (74.4)	93 (67.9)	67 (82.7)		
Undifferentiated	58 (26.6)	44 (32.1)	14 (17.3)		
Primary T-stage				3.04	0.810
T1 - T2	47 (21.6)	33 (24.1)	14 (17.3)		
T3	93 (42.7)	57 (41.6)	36 (44.4)		
T4	78 (37.7)	47 (34.3)	31 (38.3)		
N-stage				7.30	0.402
N0	31 (14.2)	19 (13.9)	12 (14.8		
N1	36 (16.5)	22 (16.1)	14 (17.3)		
N2	93 (42.7)	71 (51.8)	22 (27.2)		
N3	58 (26.6)	25 (18.2)	33 (40.7)		
TNM-stage				2.72	0.257
III	150 (68.8)	82 (59.9)	68 (84.0)		
IVa	68 (31.2)	55 (40.1)	13 (16.0)		
Total	218	137	81		

RT: Radiotherapy; IMRT: Intensity-modulated radiotherapy; CT: Chemotherapy.

There were 136 males and 82 females, with male/female ratio of 2:1. The median age of 49 years (range, 22 - 83 years). At initial diagnosis, 91 (41.7%) patients exhibited poorly differentiated carcinoma, 69 (31.7%) exhibited moderate carcinoma and 58 (26.6%) exhibited undifferentiated carcinoma. All the patients were restaged according to the International Union Against Cancer 2017 cancer staging system [11]. Overall, 150 (72.5%) patients exhibited stage III tumors, 68 (31.2%) exhibited stage IVA. According to different treatment modalities, they were divided into conventional RT plus chemotherapy (CT) group and IMRT plus chemotherapy group (IMRT + CT group).

2.2. Radiotherapy Planning and Target Volume Definition

All patients received radical RT. Patients were treated in supine position with head and shoulders immobilised in a Perspex shell or thermoplastic mask with at least five fixation points under the scanner simulation (Phillips PQS2000). Enhanced CT-scan slices measuring 3 mm were obtained from the top of the head to the arch of the aorta inferiorly. Regarding conventional RT, the combined cervico-facial field and the lower half neck field were used. After D_T 36 Gy, the spinal cord is protected and an electron beam is used to supplement the dose in the bilateral retroauricular area. After D_T 50 Gy, the volume in the bilateral retroauricular area and temporal fields was changed to 70 - 76 Gy, and the volume of enlarged lymph nodes was increased to 60 - 65 Gy. The IMRT target volume include: 1) Primary nasopharyngeal tumor (GTV); 2) Positive neck lymph nodes (GTVnd); 3) High risk clinical target volume (CTV1), and Low risk clinical target volume (CTV2). CTV1 includes GTV plus 0.5 cm radial margin, nasopharyngeal cavity, skull base, pterygopalatine fossa, internal and external pterygoid plates, nasal cavity, and posterior one-third of the maxillary sinus, para pharyngeal region, the floor of the mouth, and the elective bilateral cervical lymph node, area II. CTV2 including bilateral lower neck lymphatic drainage area III, IV and V. PTV was obtained by adding 0.3 cm margin to each target volume. Primary fields are the portals used to deliver a radiation dose to the primary site of the cancer; neck fields are additional portals used to treat cervical lymph nodes not included in the primary fields. The first-course of radiation treatment was delivered to GTV, GTVnd, CTV1, and CTV2. The prescribed dose is 61.6, 61.6, 60.0 Gy, and 53.2 Gy, respectively, in 28 fractions. In the second course, GTV was increased by 9 - 15 Gy in 3 - 5 fractions, and if there were still residual lymph nodes, the GTVnd was increased by 6 - 9 Gy in 3 - 5 fractions. The CT-scan images from the two past positioning were merged to assess the target volume and the volume of the organs at risk. The adjacent organs at risk and dose limits were of brainstem 45 - 50 Gy, spinal cord 35 - 40 Gy, optic nerve 40 - 50 Gy, pituitary gland, 40 - 55 Gy, temporal lobe 40 - 55 Gy, pinna 4 - 6 Gy, parotid gland 25 - 30 Gy, temporomandibular joint 40 - 50 Gy, and 60 - 65 Gy for the mandible. Reverse meter fins using Cadplan 6.0 or Eclipse to design 6 - 7 co-planar irradiated fields, and the treatment plan evaluation criteria were that the PTV receiving > 105% of the prescribed dose volume < 20%, <95% of the

prescribed dose volume < 3%, and no > 110% of the prescribed dose could occur anywhere outside the PTV. The IMRT treatment plan verification was performed using the IMRT Phantom model from the Swedish IBA company, the 912 dosimeter from Capintec Corporation of the United States, and the Swedish IBA company 2D ionization matrix and the Omnipro™.

2.3. Chemotherapy Regimens

The CT was administered either in induction, concomitantly with RT, or as adjuvant therapy. The three regimens are PF regimen (induction or adjuvant CT, cisplatin 70 - 80 mg/m^2 intravenous infusion on 3 days, 5 - Fluorouracil 500 - 750 mg/m^2 intravenous infusion on day 1 - 5, repeated every 3 weeks, given in 1 to 4 cycles); TP regimen (induction or adjuvant CT, cisplatin 70 - 80 mg/m^2 intravenous infusion over 3 days, paclitaxel 150 - 170 mg/m^2 intravenously on day l, repeated every 3 weeks, for 1 - 4 cycles); PF weekly regimen (cisplatin 20 mg/m^2, 5 - fluorouracil 500 mg/m^2 intravenously once/week, concurrent chemotherapy 4 - 6 cycles). The CT regimens in each group are shown in Table 2.

2.4. Follow-Up Evaluation

All of the patients were monitored weekly during the RT course for acute toxicity. Radiation oncologists reported acute toxicity of the skin, oral mucosa, and salivary glands according to the Radiation Therapy Oncology Group (RTOG) Common Terminology Criteria for Adverse Events (CTCAE) Ver. 4 criteria [12]. Patients with acute xerostomia were evaluated by attending radiation oncologists based on patients reporting as follows: Grade 0: no change over baseline; Grade 1: mild mouth dryness/slightly thickened saliva/metallic taste; Grade 2: moderate to complete dryness/thick, sticky saliva/markedly altered taste; Grade 3: severe dry mouth, no stimulation, often need to wake up at night to drink water; and Grade 4: acute salivary gland necrosis. Late injuries such as: subcutaneous soft-tissue fibrosis, difficulty in opening mouth, xerostomia, cranial nerve palsy, deafness, radiation-induced temporal lobe necrosis, visual loss, and headache were assessed by using the RTOG/European Organization for Research and Treatment of Cancer (EORTC) criteria, 6 months and 12 months after the completion of chemoradiotherapy Table 3. For all, the observation started from the first day of treatment until death or the last follow-up visit. This follow-up was undertaken until 31 December 2019, with the median follow-up period of 21.5 months (5 to 49 months). The follow-up rate was 100%.

Table 2. Chemotherapy regimen in the different groups.

Groups	PF-3 weeks	TP-3 weeks	PF-1 week	Total
Conventional RT	68	42	27	137
IMRT + CT	36	32	13	81

PF: Platinum, 5 - Fluorouracil; TP: Taxane, Platinum; RT: Radiotherapy; IMRT: Intensity-modulated radiotherapy; CT: Chemotherapy.

Table 3. Prevalence of acute and late toxicities in each group.

Treatment related toxicities	Total	Groups	
		Conventional RT + CT	IMRT + CT
	n (%)	n (%)	n (%)
Acute toxicities (n = 218 cases)			
Skin			
≤Grade 2	218 (100)	137 (62.8)	81 (37.2)
>Grade 2	0	0	0
Mucositis			
≤Grade 2	157 (72.0)	115 (83.9)	62 (76.5)
>Grade 2	41 (18.0)	22 (16.1)	19 (23.5)
Xerostomia			
≤Grade 2	185 (84.8)	119 (86.8)	66 (81.5)
>Grade 2	33 (15.2)	18 (13.2)	15 (18.5)
Late toxicities (n = 111 cases)			
Soft tissue fibrosis			
Yes	9 (8.1)	9 (12.7)	0 (0.0)
No	102 (91.9)	62 (87.3)	40 (100)
Neck hyper pigmentation			
Yes	69 (62.2)	56 (78.9)	13 (32.5)
No	42 (37.8)	15 (21.1)	27 (67.5)
Encephalopathy			
No	110 (99.1)	70 (98.6)	40 (100)
Yes	1 (0.9)	1 (1.4)	0 (0.0)
Xerostomia			
≤Grade 2	89 (80.2)	49 (69.0)	40 (100)
>Grade 2	22 (19.8)	22 (31.0)	0 (0.0)

RT: Radiotherapy; IMRT: Intensity-modulated radiotherapy; CT: Chemotherapy.

2.5. Statistical Analysis

All analysis was performed using SPSS 23.0 (SPSS Inc, Chicago, IL). The Chi-square tests were used to compare the baseline characteristics between the two groups. The Kaplan-Meier methods were used to estimate the survival. Log-rank tests were used to compare the survival. The level of significance was set as $P < 0.05$.

3. Results

3.1. Tumor Response to Treatment and Failure Pattern

Patient and tumor characteristics are shown in Table 1. All patients had histo-

logically confirmed NPC. Based on the intention-to-treat, and analyze, residual tumor in the primary tumor site was observed in 11 patients six months after the end of treatment including, conventional RT + CT group 9 cases and 2 case in IMRT + CT group; residual neck lymph nodes 4 cases including, IMRT + CT group 1 case and 3 cases in conventional RT + CT group. During the follow-up period, 3 patients experienced recurrence in primary site including, conventional RT + CT group 3 cases and 0 cases in IMRT + CT group; neck lymph nodes 4 cases including, conventional RT + CT group 3 cases and 1 cases in IMRT + CT group. Distant metastases 10 cases including, IMRT + CT group 3 case and 7 cases in conventional RT + CT group. A total there were 14 deaths, including conventional RT + CT group 11 cases and 3 cases in IMRT + CT group. For the whole group and in each group of patients, LRFS, DMFS, and the OS rates are shown in Table 4.

3.2. Acute Reactions and Late Toxicities

The acute and late toxicity profile of conventional RT + CT and IMRT + CT is listed in Table 3. Acute toxic reactions were assessed in all of the 218 (100%) patients. Grade 0 - 2 skin reactions were seen in all patients. There were no > Grade 2 acute skin reaction. Among patients with acute oral and pharyngeal mucosa reactions, eight patients with grade 3 acute reactions in the oral and pharyngeal mucosa interrupted treatment for more than 5 days. Of these, 7 cases in the conventional RT + CT group and 1 case in the IMRT + CT group, all others completed treatment as planned. 33 (15.2%) patients developed acute xerostomia, including 18 (13.2%) patients in conventional RT + CT group, and 15 (18.5%) patients in IMRT group. The common late injury in patients more than 1 year after the end of treatment is skin change, subcutaneous soft tissue fibrosis, xerostomia, etc. One patient in conventional RT + CT group developed radiation encephalopathy 8 months after treatment. Among the 111 patients who were followed up for more than 1 year, the occurrence of xerostomia in each group 12 months after treatment is shown in Table 3.

Table 4. The treatment effect in the whole group and in each group.

Groups	LRFS (%)		DMFS (%)		OS (%)	
	2 years	3 years	2 years	3 years	2 years	3 years
All	92	80	84	72	87	81
Conventional RT + CT	76	71	71	68	77	65
IMRT + CT	97	88	84	84	100	100

LRFS: Locoregional relapse-free survival; DMFS: Distance metastases-free survival; OS: Overall survival; RT: Radiotherapy; IMRT: Intensity-modulated radiotherapy; CT: Chemotherapy; ($\chi^2 = 5.06$, P = 0.028).

4. Discussion

It is widely accepted that conventional RT has always been controversial in head and neck cancer [13], especially for conventional RT of the nasopharynx. The ability to sculpt the dose to the target volume has resulted in significant toxicity, and the risk of permanent feeding tube dependence with conventional RT is high during and after irradiation. Compared with the more morbid severe oropharyngeal mucositis, xerostomia, soft tissue fibrosis, dysphagia with conventional RT, IMRT has been routine choice in the past three decade [14]. In This article, we reported the outcome of 218 NPC who underwent definitive RT with conventional RT + CT and IMRT + CT. We found that not only was the treatment outcome improved, but at the same time treatment-related toxicity was significantly reduced by IMRT. For all outcome parameters, 2-year LRFS, 76% vs 97%; DMFS, 71% vs 84%; OS, 77% vs 100%, 3-year LRFS 71% vs 88%, DMFS, 68% vs 84%; OS, 65% vs 100% (χ^2 = 5.06, P = 0.028), and one-year treatment-related toxicities > Grade 2 xerostomia 31.0% vs 0%, soft tissue fibrosis 12.7% vs 0%, neck hyperpigmentation 78.9% vs 32.5% confirmed these findings. Chua *et al.* [15] analyzed 784 cases of NPC in phase III clinical trials. The data showed that the 5-year recurrence-free survival was 63.5% and 58.1% in the chemoradiotherapy group and the RT group, respectively (P < 0.05). In contrast, the 5-year OS rate was not significantly improved (61.9%: 58.1%, P = 0.092). Zhang B *et al.* [16], and Fang L *et al.* [17] also analyzed the results of 6 randomized controlled trials and concluded that conformal RT combined with platinum-based CT may be beneficial for patient with locally advanced NPC survival. However, the study results did not confirm the benefit of the RT regimen. Several meta-analysis from USA assessed the effect of chemoradiotherapy on the outcome of treatment of locally advanced NPC, the results showed that the combined chemoradiotherapy group was more effective than RT alone [18] [19]. The 2 and 3-year survival rates were increased by 20% and 19%, respectively, and the 2 and 3-year disease-free survival rates were increased by 37% and 40%, respectively (P < 0.05). As in our study, the combination chemoradiotherapy in this group of studies included neoadjuvant chemotherapy, concurrent chemotherapy, and induction chemotherapy [20] [21] [22]. The comparison of patients' LRFS, DMFS and OS suggested that CT provided a small but statistically significant benefit and that the combination of different CT and RT regimens was not statistically significant between groups. On behalf of our results, we believe that, the benefit in OS appears to be more significant when the CT drugs are given concurrently with IMRT. This model has become the standard treatment model for patients with stage III and IV NPC in the United States since the first prospective randomized controlled Intergroup Study comparing concurrent chemoradiotherapy plus adjuvant CT with RT alone showed significant improvement in survival [23] [24]. O'Meara *et al.* [25] analyzed the results of 5 randomized phase III clinical studies, further affirmed the benefit of chemoradiotherapy over RT alone, and recommended platinum-based chemoradiotherapy plus adjuvant

CT for locally advanced NPC as a standard treatment. Unlike our study, the combination of CT and RT was not randomised, and the pairwise combination mode of neoadjuvant CT, concurrent CT and induction CT were not used. Therefore, it is difficult to draw certain conclusions as no difference was seen in the survival comparison between the RT plus CT group and the RT alone group. They only considered that it may be related to the shorter follow-up period, inconsistent CT dosing regimen, and the timing of administration. In our current study, the couple IMRT + CT had the best effect, suggesting that changes in RT techniques may be helpful to improve the survival rate of patients. Given that, the anatomical location of NPC is close to the midline of the body and surrounded by many adjacent and vital organs that need to be protected. This is the main reason why conventional RT techniques cannot pass through the tumor area at high doses. Furthermore, the biological characteristics of NPC require a simultaneous and different radiation dose splitting in the primary tumor, surrounding high-risk lymph nodes metastasis areas, and positive lymphatic drainage areas (**Figure 1**). Although conventional RT can cover the treatment range within the irradiation range, it cannot avoid the target inhomogeneity of dose distribution within the region. At first sight, as a model of high-precision RT, IMRT has the advantage of high dose and good target conformity, so that a high therapeutic dose can be concentrated on the tumor site, while the normal tissue around the tumor is less irradiated. Secondly, IMRT can achieve a simultaneous accelerated radiation therapy boost (simultaneous integrated boost radiotherapy (SIB-RT), which is essential to increase the dose per fraction of the target area to improve the biological effect. Studies have shown that a single prescription dose increase from 2 Gy to 2.5 Gy results in a 25% increase in physical dose and a 40% increase in biological dose [26].

Besides in our study, the total dose of IMRT and conventional RT to the nasopharynx was equivalent, and there were no recurrences in the primary site after treatment. However, in IMRT group, we observed 1 case of cervical lymph node recurrence (4 cases in the whole group), and 3 cases of distant metastasis (10 in the whole group) after treatment, indicating that IMRT may be more effective than conventional RT in terms of local tumor control. Another reason for the use of IMRT in the treatment of NPC is the preservation of parotid gland function. The incidence of severe xerostomia after conventional RT is nearly 100%, and IMRT technology can significantly reduce the volume and the exposure of the salivary gland to the radiation dose, so the incidence of dry mouth is reduced, the secretion function of the salivary gland gradually recovers over time, and the patient's quality of life change is extremely high [26] [27] [28]. These findings are consistent with those in our research work. However, the present study has some limitations. First, all of the inclusion has been only retrospectively conducted. Second, the exact and objective clinical value of this additional xerostomia sparing remains unclear. A prospective trial, including objective salivary gland secretion evaluation and patient-reported outcomes, could

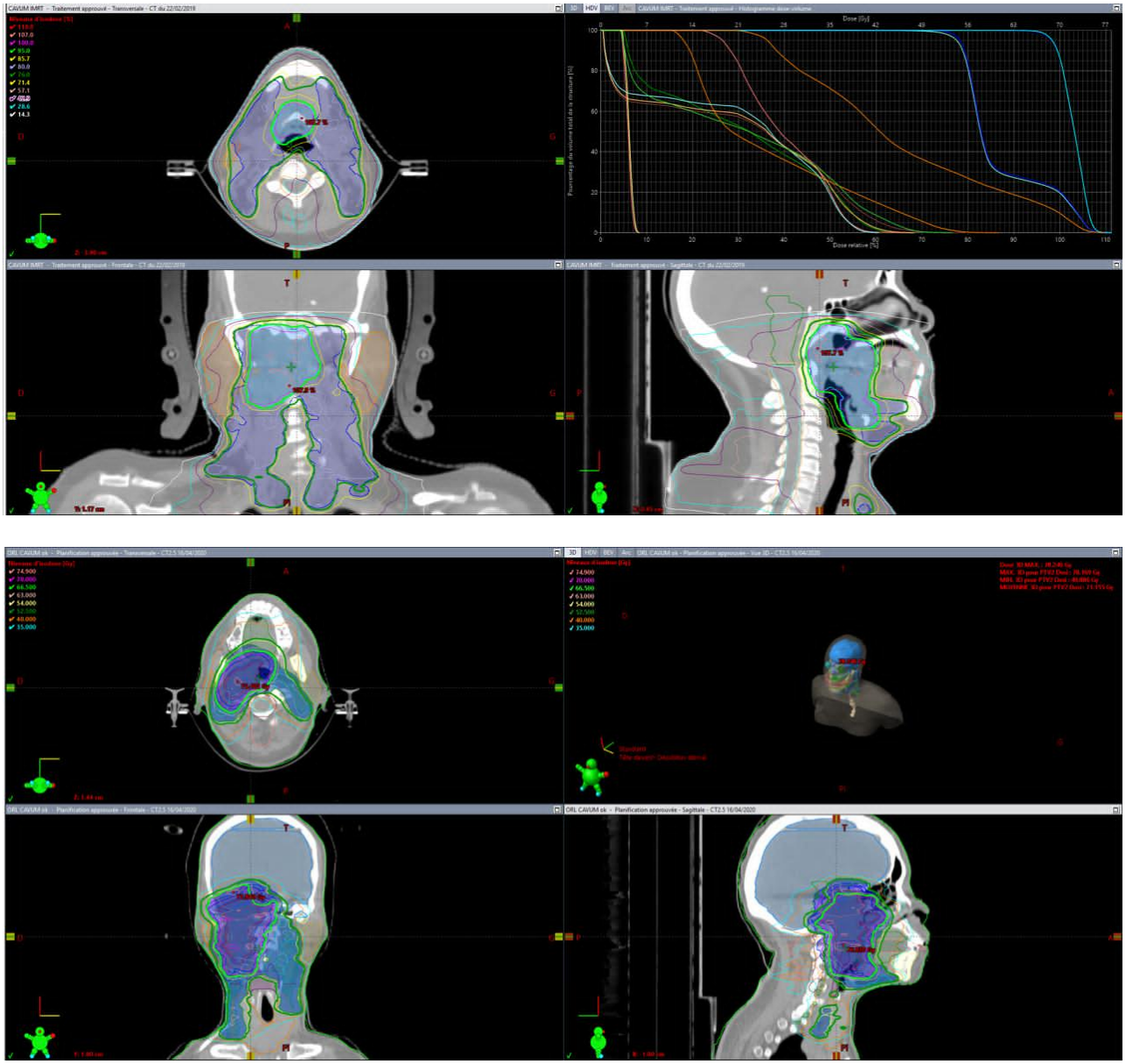

Figure 1. Target volume coverage using IMRT planning system in nasopharyngeal carcinoma.

better investigate the added value of our findings. Finally, the original plans have not been developed with the same technique, using both conventional RT + CT and IMRT + CT methods. Nevertheless, to the best of our knowledge, this is one of the first studies investigating the prevalence of xerostomia using IMRT and CT for a strictly homogeneous cohort of patients, all treated for locally advanced nasopharyngeal carcinomas in our cancer center. According to the characteristics of Chinese NPC, which is mainly poorly differentiated squamous cell carcinoma with a high probability of distant metastases, our results further illustrates that the combination of IMRT and CT may be the direction of efforts for these population of patients with NPC. Therefore, in our ongoing studies comparing the efficacy of IMRT alone and IMRT + CT, the optimal timing CT and RT, and

the choice of regimens are all worthy of extensive, in-depth discussions.

5. Conclusion

Compared to conventional RT + CT, CT combined with IMRT may not only improve LRFS, DMFS and OS, but can also significantly reduce treatment-related toxicity in patients treated for locally advanced stage III-IV nasopharyngeal carcinoma. However, the optimal choice of CT regimens needs to be further studied in large samples.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Keita M. and Li Juan drafted the manuscript and participated in data collection, and helped to analyze the data. Shen Wen Bin participated in the coordination of the study. All authors read and approved the final manuscript.

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