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Head and Neck Cancers

10-Year Results of Therapeutic Ratio by Intensity-Modulated Radiotherapy Versus Two-Dimensional Radiotherapy in Patients with Nasopharyngeal Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Nasopharyngeal carcinoma • Intensity-modulated radiotherapy • Two-dimensional radiotherapy • 10-year results • Therapeutic ratio

Abstract

Background. The purpose of this study was to verify 10-year results of survival and late toxicities and assess the ultimate therapeutic ratio of intensity-modulated radiotherapy (IMRT) versus two-dimensional radiotherapy (2DRT) in patients with nasopharyngeal carcinoma (NPC).

Materials and Methods. We retrospectively reviewed the data from 1,276 patients with nonmetastatic NPC who received IMRT or 2DRT from January 2003 to December 2006.

Results. Of the 1,276 patients, 512 were treated with IMRT and 764 with 2DRT. Median follow-up was 115 months. At 10 years, the IMRT group demonstrated significantly better results than the 2DRT group in local failure-free survival (L-FFS; 90% vs. 84%; hazard ratio [HR], 0.57, 95% confidence interval [CI], 0.40–0.81; $p = .001$), failure-free survival (FFS; 69% vs. 58%; HR, 0.69, 95% CI, 0.57–0.83; $p < .001$), and overall survival (OS; 75% vs. 63%; HR, 0.62, 95% CI, 0.51–0.77; $p < .001$). Subgroup multivariate analyses showed that radiotherapeutic technique (IMRT vs. 2DRT) remained an independent prognostic factor for L-FFS in the T1 subgroup (HR, 0.30; 95% CI, 0.11–0.80; $p = .02$); for FFS in the stage II subgroup (HR, 0.42; 95% CI, 0.24–0.73; $p = .002$); and for OS in the stage I (HR, 0.20; 95% CI, 0.04–0.96; $p = .04$), stage II (HR, 0.39; 95% CI, 0.21–0.75; $p = .004$), and stage IVA–B (HR, 0.74, 95% CI, 0.56–0.98; $p = .04$) subgroups. The incidence of grade 3–4 temporal lobe necrosis, cranial neuropathy, eye damage, ear damage, neck soft tissue damage, trismus, and dry mouth was significantly lower in the IMRT group than in the 2DRT group.

Conclusion. IMRT demonstrated an improved ultimate therapeutic ratio compared with 2DRT in patients with NPC after a 10-year follow-up, with significant improvement of L-FFS, FFS, and OS and decrease in most late toxicities. ***The Oncologist*** 2019;24:e38–e45

Implications for Practice: The ultimate therapeutic ratio of intensity-modulated radiotherapy versus two-dimensional radiotherapy in patients with nasopharyngeal carcinoma is unclear. In this retrospective study of 1,276 patients with nonmetastatic nasopharyngeal carcinoma with a follow-up of 115 months, intensity-modulated radiotherapy demonstrated an improved ultimate therapeutic ratio compared with two-dimensional radiotherapy, with significant improvement of local failure-free survival, failure-free survival, and overall survival and decrease in most late toxicities and noncancer deaths. However, distant control remains insufficient with this treatment modality.

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Introduction

Radiotherapy is the primary treatment modality for nondisseminated nasopharyngeal carcinoma (NPC). Treatment with two-dimensional radiotherapy (2DRT) transitioned to three-dimensional conformal radiotherapy, and in particular to intensity-modulated radiotherapy (IMRT), has represented a major step forward in the treatment of NPC [1]. Numerous studies have reported beneficial IMRT results for the treatment of NPC [1–3]; however, few comparison studies of the effects of IMRT versus 2DRT on outcomes in NPC exist.

We therefore performed a retrospective study to directly compare IMRT versus 2DRT results in patients with NPC treated in the same time period. After a median follow-up period of 53 months, preliminary results demonstrated that the greater improvement in treatment results with IMRT than with 2DRT was primarily by achieving a higher local tumor control rate in patients with NPC, especially in the early T classification patients [4]. However, it should be noted that this follow-up period was not long enough, especially to study overall survival (OS), and there were no data on detailed late toxicities at that time.

On the other hand, time to relapse after IMRT might be postponed compared with 2DRT. The study on IMRT showed that more than half of observed local relapses occurred after 2 years [5]. Moreover, advances in salvage treatment after initial treatment failure, including surgery, reirradiation, and chemotherapy, cannot be ignored, and this was associated with better OS than before [6, 7]. In addition, although progression-free survival could be a valid surrogate endpoint for OS based on the results of our meta-analysis, it does not reduce the need for long-term follow-up of patients, because some unexpected adverse effects that might occur later would not be captured by the surrogate endpoints [8]. Hence, the purpose of this long-term follow-up was to verify 10-year results of survival and late toxicities and to further assess the ultimate therapeutic ratio of IMRT versus 2DRT in patients with NPC.

Materials and Methods

Patient Characteristics

A total of 1,276 patients with newly diagnosed, biopsy-proven, nonmetastatic NPC presented at Sun Yat-Sen University Cancer Center between January 2003 and December 2006 and were included in this study. All patients underwent physical examination, fiberoptic examination, chest x-ray, abdominal ultrasonography, and magnetic resonance imaging prior to treatment. Patients with stage N2–N3 disease underwent single photon emission computed tomography for whole body bone scanning. For stage and classification, the seventh edition of the Union for International Cancer Control (UICC) staging system was used [9]. Our protocol was approved by the ethics committee of Sun Yat-Sen University Cancer Center.

Treatment

All patients were treated with definitive-intent radiation therapy, with 512 (40%) patients treated with IMRT and 764 (60%) patients treated with 2DRT. In cases of documented persistent disease or relapse, salvage treatments, including intracavitary brachytherapy, surgery, reirradiation, and chemotherapy, were provided, if applicable.

2DRT. Patients were immobilized in supine position with a thermoplastic mask and treated with two lateral-opposing faciocervical portals to irradiate the nasopharynx and the upper neck in one volume, followed by application of the shrinking-field technique to limit irradiation of the spinal cord. An anterior cervical field was used to treat the neck with a laryngeal block. The accumulated radiation doses were 68–76 Gy (median, 70 Gy), with 2 Gy per fraction applied to the primary tumor, 60–66 Gy applied to the involved areas of the neck, and 50 Gy applied to the uninvolved areas. All patients were treated with one fraction daily for 5 days per week.

A boost portal was performed if necessary. Patients with bulky parapharyngeal disease in the 2DRT group received the parapharyngeal boost technique [10]. A boost dose (8–12 Gy per four to six fractions) was delivered to the skull base in patients with NPC involving the skull base and intracranial extension. Intracavitary afterloading treatment with iridium-192 was used to address local persistence 2–3 weeks after external radiotherapy with 12–16 Gy per three to five fractions once every 2 days in 1–2 weeks. Any palpable residual nodes presenting after external radiotherapy were boosted to 70 Gy.

IMRT. Immobilization for IMRT was the same as for 2DRT. Computed tomography after administration of intravenous contrast medium was performed by collection of 3 mm slices from the head to the level of 2 cm below the sternoclavicular joint. The primary tumor and the upper neck above the caudal edge of the cricoid cartilage were treated with IMRT. The target volumes were delineated using an institutional treatment protocol previously described [11], which was in accordance with the International Commission on Radiation Units and Measurements Reports 50 and 62. The clinical target volumes (CTVs) were individually delineated on the basis of the tumor invasion pattern [12]. The contoured image was transferred to CORVUS 3.0, an inverse IMRT planning system (Peacock) developed by Best NOMOS Corporation (Pittsburgh, PA). The radiation dose prescribed as per protocol was defined as follows: 2.27 Gy per fraction to the planning target volume (PTV) of gross tumor volume of the primary (GTV-P), 60–66 Gy to the PTV of nodal gross tumor volume (GTV-N), 60 Gy to the PTV of CTV-1 (i.e., high risk regions), 54 Gy to PTV of CTV-2 (i.e., low-risk regions) and CTV-N (i.e., neck nodal regions). The treatment was delivered by a dynamic, multileaf, intensity-modulating collimator. For the lower neck, an anterior cervical field was used. All patients were treated with one fraction daily over 5 days per week. Patients with local tumor persistence 2–3 weeks after IMRT received additional intracavitary irradiation, as described for the 2DRT group.

Chemotherapy. Of the 881 patients with stage III or IVA–B disease, 699 (79%) received neoadjuvant, concomitant, and/or adjuvant chemotherapy using various regimens of cytotoxic drugs (all cisplatin-based; supplemental online Table 1).

Table 1. Characteristics of the patients

Characteristic	IMRT group (n = 512), n (%)	2DRT group (n = 764), n (%)	p value[a]
Gender			.28
Male	393 (77)	566 (74)	
Female	119 (23)	198 (26)	
Age, years			.17
≤60	472 (92)	687 (90)	
>60	40 (8)	77 (10)	
Histology			.13
WHO type I	3 (1)	5 (1)	
WHO type II–III	503 (98)	757 (99)	
Clinical stage[b]			
T classification T3–T4	272 (53)	441 (58)	.11
N classification N2–N3	169 (33)	232 (30)	.32
Stage III–IVB	347 (68)	534 (70)	.42
Chemotherapy in stage III–IV patients	281 (81)	418 (78)	.33

[a]p values were calculated by the chi-square test.
[b]The 7th edition of the Union for International Cancer Control staging system.
Abbreviations: 2DRT, two-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy; WHO, World Health Organization.

Follow-Up

The duration of patient follow-up was measured from the first day of therapy to either the day of last examination or the day of death. Patients were seen every 3 months during the first 2 years and every 6 months thereafter until death.

Statistical Analysis

The following endpoints were assessed: local failure-free survival (L-FFS), regional failure-free survival (R-FFS), distant failure-free survival (D-FFS), failure-free survival (FFS), OS, and late toxic effects. We calculated L-FFS, R-FFS and D-FFS from the date of commencement of therapy to the date of the first local, regional, or remote failure, respectively. FFS was calculated from therapy to the date of treatment failure or death from any cause, whichever was first, and OS was from therapy to death. We graded late toxic effects in accordance with the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer [13].

Time-to-event data were described with the Kaplan-Meier curves, and time-to-event intervals were compared using the log-rank test. We calculated hazard ratios (HRs) with the Cox proportional hazards model. We did multivariable analyses with the Cox proportional hazards model to test the independent significance of different factors. Covariates included host factors (i.e., sex and age), tumor factors (i.e., T and N classification), radiotherapy technique (IMRT vs. 2DRT), and chemotherapy (yes vs. no). We compared toxicity rates and other categorical variables using the χ^2 test (or Fisher's exact test, if indicated). All tests were two-sided; we deemed p values of less than .05 to be significant. All analyses were done with Stata (version 10; StataCorp, College Station, TX).

Results

Patient Characteristics

The last follow-up was December 5, 2016, and the median follow-up for the entire cohort was 115 months (range, 2–161 months). There were no significant differences in the host factors, histological categories, tumor factors, or chemotherapy between the IMRT and 2DRT groups (Table 1, supplemental online Table 2).

Overall Pattern of Failure

Overall, 422 (33%) patients experienced failure at one or more sites. Distant failure alone was the most common incidence (16%), followed by local failure alone (9%; supplemental online Table 3).

Local Control

At 10 years, the IMRT group demonstrated significantly better L-FFS than the 2DRT group (90% vs. 84%; HR, 0.57; 95% confidence interval [CI], 0.40–0.81; p = .001; Table 2). Multivariate analysis showed that the radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for L-FFS (HR, 0.60; 95% CI, 0.42–0.85; p = .004; Table 3).

After stratification by T classification, 10-year L-FFS rates were higher in the IMRT group than the 2DRT group, but statistical significance could be reached only for the T1 classification patients, and borderline significance was observed in T4 patients (Table 2 and Fig. 1). Further subgroup multivariate analyses showed that radiotherapeutic technique (IMRT vs. 2DRT) only remained an independent prognostic factor for L-FFS in T1 patients (HR, 0.30; 95% CI, 0.11–0.80; p = .02) and was a marginally significant predictive factor in T4 patients (HR, 0.66; 95% CI, 0.41–1.07; p = .09; supplemental online Table 4).

Regional Control

The 10-year R-FFS rates were 95% for the IMRT group and 94% for the 2DRT group (HR, 0.69; 95% CI, 0.41–1.16; p = .16; Table 2). Multivariate analysis failed to demonstrate that the radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for R-FFS (Table 3). After stratification by N classification, no significant differences were observed between the IMRT and 2DRT groups in all N0–N3 classifications by univariate and multivariate analyses (Table 2 and supplemental online Table 4).

Distant Control

The 10-year D-FFS rate was 80% in the IMRT group and 79% in 2DRT group (HR, 0.96; 95% CI, 0.74–1.23; p = .72; Table 2). Multivariate analysis failed to demonstrate that the radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for D-FFS (Table 3). After stratification by N classification, no significant differences were observed between the IMRT and 2DRT groups in all N0–N3 classifications with univariate and multivariate analyses (Table 2 and supplemental online Table 4).

Disease Control

The 10-years FFS rates for the IMRT and 2DRT groups were 69% and 58%, respectively (HR, 0.69; 95% CI, 0.57–0.83;

Table 2. Survival

Variable	10-year survival rate, %		Hazard ratio[a] (95% CI)	*p* value[b]
	IMRT group	2DRT group		
Local failure-free survival				
T1	97	90	0.31 (0.12–0.84)	.02
T2	94	89	0.56 (0.17–1.83)	.34
T3	90	86	0.73 (0.36–1.48)	.37
T4	81	72	0.63 (0.39–1.01)	.05
All T classifications	90	84	0.57 (0.40–0.81)	.001
Regional failure-free survival				
N0	98	98	1.66 (0.15–18.4)	.68
N1	95	93	0.77 (0.38–1.57)	.47
N2	95	93	0.55 (0.19–1.61)	.27
N3	90	89	0.83 (0.21–3.31)	.79
All N classifications	95	94	0.69 (0.41–1.16)	.16
Distant failure-free survival				
N0	92	90	0.78 (0.30–2.01)	.60
N1	81	82	1.10 (0.75–1.60)	.63
N2	76	71	0.84 (0.53–1.33)	.45
N3	53	58	1.16 (0.64–2.10)	.63
All N classifications	80	79	0.96 (0.74–1.23)	.72
Failure-free survival				
Stage I	93	83	0.41 (0.12–1.35)	.13
Stage II	85	70	0.44 (0.25–0.77)	.003
Stage III	69	63	0.81 (0.58–1.14)	.23
Stage IVA–B	51	42	0.75 (0.58–0.98)	.03
All stages	69	58	0.69 (0.57–0.83)	<.001
Overall survival				
Stage I	96	85	0.22 (0.05–1.03)	.04
Stage II	89	77	0.43 (0.23–0.81)	.01
Stage III	79	67	0.63 (0.43–0.94)	.02
Stage IVA–B	56	46	0.71 (0.54–0.94)	.02
All stages	75	63	0.62 (0.51–0.77)	<.001

[a]Hazard ratios were calculated by an unadjusted Cox proportional hazards model.
[b]*p* values were calculated by an unadjusted log-rank test.
Abbreviations: 2DRT, two-dimensional radiotherapy; CI, confidence interval; IMRT, intensity-modulated radiotherapy.

$p < .001$; Table 2). Multivariate analysis showed that the radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for FFS (HR, 0.72; 95% CI, 0.59–0.87; $p = .001$; Table 3).

After stratification by the stage, 10-year FFS rates were higher in the IMRT group than the 2DRT group, but statistical significance could be reached only for the stage II and stage IVA–B patients (Table 2). Further subgroup multivariate analyses showed that radiotherapeutic technique (IMRT vs. 2DRT) only remained an independent prognostic factor for FFS in stage II patients (HR, 0.42; 95% CI, 0.24–0.73; $p = .002$) and was a marginally significant predictive factor in stage I (HR, 0.35; 95% CI, 0.10–1.19; $p = .09$) and stage IVA–B (HR, 0.78; 95% CI, 0.60–1.02; $p = .07$) patients (supplemental online Table 4).

Overall Survival

At 10 years, the IMRT group demonstrated significantly better OS than the 2DRT group (75% vs. 63%; HR, 0.62; 95% CI, 0.51–0.77; $p < .001$; Table 2). Multivariate analysis showed that the radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for OS (HR, 0.66; 95% CI, 0.53–0.81, $p < .001$; Table 3).

After stratification by the stage, 10-year OS rates were higher in the IMRT group than the 2D-CRT group, and statistical significance could be reached for each stage patients (Table 2 and Fig. 2). Further subgroup multivariate analyses showed that radiotherapeutic technique (IMRT vs. 2DRT) was an independent prognostic factor for OS in stage I (HR, 0.20; 95% CI, 0.04–0.96; $p = .04$), stage II (HR, 0.39; 95% CI, 0.21–0.75; $p = .004$), and stage IVA–B (HR, 0.74; 95% CI, 0.56–0.98; $p = .04$) patients and a marginally

Table 3. Summary of prognostic factors multivariable analyses

Endpoints by variables	Hazard ratio (95% CI)	*p* value[a]
Local failure-free survival		
Gender, female vs. male	0.55 (0.36–0.85)	.007
Age, >60 years vs. ≤60 years	1.52 (0.96–2.41)	.07
T classification, T3–4 vs. T1–2	2.90 (1.95–4.32)	<.001
N classification, N2–3 vs. N0–1	1.17 (0.83–1.64)	.38
Chemotherapy, yes vs. no	0.93 (0.64–1.37)	.73
RT technique, IMRT vs. 2DRT	0.60 (0.42–0.85)	.004
Regional failure-free survival		
Gender, female vs. male	0.64 (0.33–1.22)	.18
Age, >60 years vs. ≤60 years	1.41 (0.64–3.12)	.40
T classification, T3–4 vs. T1–2	0.54 (0.32–0.91)	.02
N classification, N2–3 vs. N0–1	1.40 (0.83–2.39)	.20
Chemotherapy, yes vs. no	1.79 (0.98–3.30)	.06
RT technique, IMRT vs. 2DRT	0.65 (0.39–1.11)	.12
Distant failure-free survival		
Gender, female vs. male	0.85 (0.63–1.15)	.30
Age, >60 years vs. ≤60 years	1.27 (0.84–1.92)	.25
T classification, T3–4 vs. T1–2	1.57 (1.19–2.08)	.001
N classification, N2–3 vs. N0–1	2.14 (1.66–2.76)	<.001
Chemotherapy, yes vs. no	1.51 (1.09–2.09)	.01
RT technique, IMRT vs. 2DRT	0.94 (0.73–1.22)	.65
Failure-free survival		
Gender, female vs. male	0.81 (0.65–1.00)	.05
Age, >60 years vs. ≤60 years	1.72 (1.33–2.23)	<.001
T classification, T3–4 vs. T1–2	1.84 (1.50–2.26)	<.001
N classification, N2–3 vs. N0–1	1.52 (1.26–1.83)	<.001
Chemotherapy, yes vs. no	1.25 (1.00–1.60)	.048
RT technique, IMRT vs. 2DRT	0.72 (0.59–0.87)	.001
Overall survival		
Gender, female vs. male	0.83 (0.66–1.05)	.13
Age, >60 years vs. ≤60 years	2.13 (1.64–2.78)	<.001
T classification, T3–4 vs. T1–2	1.94 (1.55–2.44)	<.001
N classification, N2–3 vs. N0–1	1.56 (1.27–1.91)	<.001
Chemotherapy, yes vs. no	1.26 (0.99–1.61)	.06
RT technique, IMRT vs. 2DRT	0.66 (0.53–0.81)	<.001

[a]*p* values were calculated using an adjusted Cox proportional-hazards model. The following parameters were included in the model as the covariates for each analysis: gender, age (≤60 years vs. >60 years), T classification (T1–2 vs. T3–4), N classification (N0–1 vs. N2–3), chemotherapy (no vs. yes), and RT technique (2DRT vs. IMRT).

Abbreviations: 2DRT, two-dimensional radiotherapy; CI, confidence interval; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

significant predictive factor in stage III patients (HR, 0.69; 95% CI, 0.46–1.03; $p = .07$; supplemental online Table 4).

The IMRT group had a significant reduction in the 10-year actuarial incidence of death from disease progression compared with the 2DRT group (21% vs. 31%; HR, 0.64; 95% CI, 0.51–0.81; $p < .001$); moreover, the 10-year actuarial incidence of death from treatment-related toxicities, incidental causes, or unknown reasons was significantly lower in the IMRT group compared with the 2DRT group (5% vs. 8%; HR, 0.55; 95% CI, 0.34–0.90; $p = .02$).

Late Toxicities

Overall, 91 (18%) of 512 patients in the IMRT group and 255 (33%) of 764 patients in the 2DRT group developed one or more late grade 3–4 toxicities ($p < .001$). One (0.2%) of 512 patients in the IMRT group died from temporal lobe necrosis, and 8 (1%) of 764 patients in the 2DRT group died from temporal lobe necrosis, cranial neuropathy, and/or trismus ($p = .08$). The incidence of grade 3–4 temporal lobe necrosis, cranial neuropathy, eye damage, ear damage, neck soft tissue damage, trismus, and dry mouth was significant lower in the IMRT group compared with the 2DRT group (Table 4).

Discussion

As in our previous study, better local control with IMRT was demonstrated in patients with NPC in the current study, especially in the T1 patients. We hypothesize that this improvement was mainly due to escalation of the applied radiation dose, because there is a dose-response relationship between tumor control and radiation dose [14]. IMRT can reach dose escalation with reasonable safety for better dose differential between tumor and normal tissues [1]. Meanwhile, IMRT showed a trend to improve local control in T4 patients, which was not shown in our previous study. With the long-term follow-up in the current study, we observed almost all local relapses, only half of which occurred in 2 years after treatment. According to the findings of our previous study, local control of T3–4 patients in the 2DRT group increased when they received additional boost therapy. Thus, improvement in local control of T3–4 patients in the IMRT group caused by dose escalation was diminished compared with that of the 2DRT group receiving additional boost treatment. However, it might be hard to attain satisfying local control with 2DRT plus boost therapy in patients with extensive primary tumors (T4 patients), because its dose and coverage often had to be compromised in order to avoid unacceptable complications [15]. Alternatively, IMRT could provide a high dose to target area of T4 patients while significantly sparing nearby critical normal tissues [2]. As shown in the current study, the incidence of grade 3–4 temporal lobe necrosis, cranial neuropathy, eye damage, ear damage, trismus, and dry mouth was significant higher in the 2DRT group than in the IMRT group.

IMRT did not improve regional control compared with 2DRT. Both groups reached excellent regional control because of the biological character of metastatic neck nodes [16]. However, it was remarkable that toxicity was different between these two treatments, and 2DRT was associated with more severe neck soft tissue damage. Moreover, IMRT did not improve distant control of all N classifications patients. The current study showed that distant metastasis as the only site of failure (206/1,276 patients, 16%) was much more common than distant metastasis with other sites of failure (53/1276 patients,

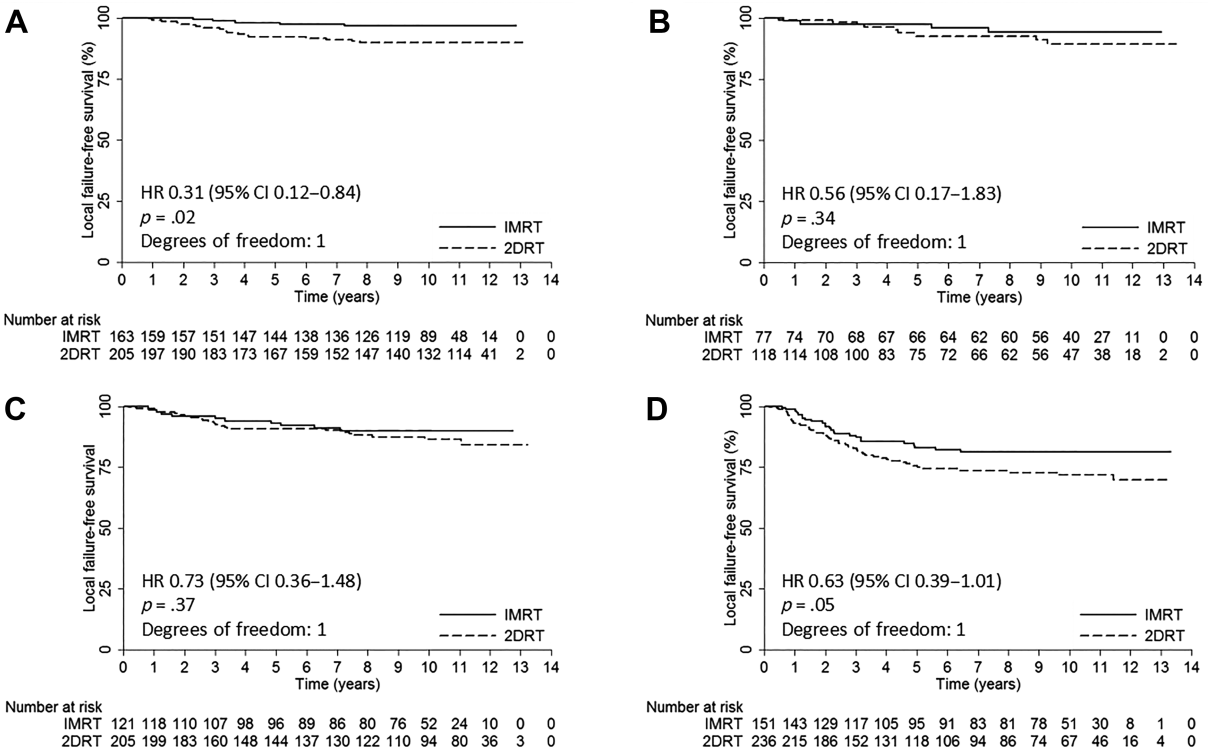

Figure 1. Kaplan-Meier local failure-free survival curves for the IMRT group and the 2DRT group. **(A)**: T1 classification. **(B)**: T2 classification. **(C)**: T3 classification. **(D)**: T4 classification. HRs were calculated by the unadjusted Cox proportional hazards model. *P* values were calculated by the unadjusted log-rank test.
Abbreviations: 2DRT, two-dimensional radiotherapy; CI, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

Table 4. Grade 3–4 late adverse events

Late adverse event	IMRT group (*n* = 512), *n* (%)	2DRT group (*n* = 764), *n* (%)	*p* value[a]
Temporal lobe necrosis	10 (2)	30 (4)	.047
Cranial neuropathy	16 (3)	47 (6)	.01
Eye	3 (1)	17 (2)	.02
Ear (hearing impairment/otitis)	52 (10)	128 (17)	.001
Bone necrosis	0 (0)	2 (0.3)	.25
Neck soft tissue damage	7 (1)	39 (5)	<.001
Trismus	3 (1)	19 (2)	.01
Dry mouth	17 (3)	56 (7)	.003

[a]*p* values were calculated by the chi-square test.
Abbreviations: 2DRT, two-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy.

4%). This means that NPC has a higher probability of micrometastatic dissemination at the time of initial diagnosis. The effect of local control on D-FFS will be small until effective methods to detect and treat subclinical distant metastasis before radiotherapy are developed.

As a result of the higher L-FFS rate achieved by IMRT in T1 patients, FFS of stage II disease was significantly improved, and the improvement in stage I was of borderline significance. Therefore, improvement of OS in early-stage disease with IMRT was primarily due to achieving a higher local control rate. Meanwhile, a marginal improvement in FFS was also observed in stage IVA–B patients treated with IMRT, mainly because IMRT had a trend to improve local control in T4 patients. Furthermore, IMRT demonstrated a significant effect on risk of most late toxicities compared with the 2DRT, especially in locoregionally advanced NPC. It had a significant reduction in the 10-year actuarial incidence of noncancer death. Therefore, significantly better OS was achieved by IMRT in stage IVA–B patients, and marginal improvement was observed in stage III patients.

In a randomized trial conducted by Peng et al. with a follow-up of only 42 months, IMRT was proved to provide improved local control, especially in patients with late-stage NPC [17]. Unlike in our study, the improvement of local control in the IMRT group for early T classification patients in their study was not remarkable. It was hypothesized that excellent local control provided by 2DRT plus boost therapy in early T classification patients led to this result. Furthermore, different staging systems used in Peng et al.'s and our studies might also contribute to the discrepancy, because T classifications changed from the sixth to the seventh edition of the UICC staging system. In another retrospective study by Zhang et al. with a larger cohort and follow-up of only 49 months, the results showed that IMRT significantly improved local, locoregional, and disease control compared with 2DRT for nondisseminated NPC [18]. However, no significant advantage was observed in OS when IMRT was used, which was not consistent with our results. We attributed this mainly to the relatively immature follow-up period for OS. With changes in

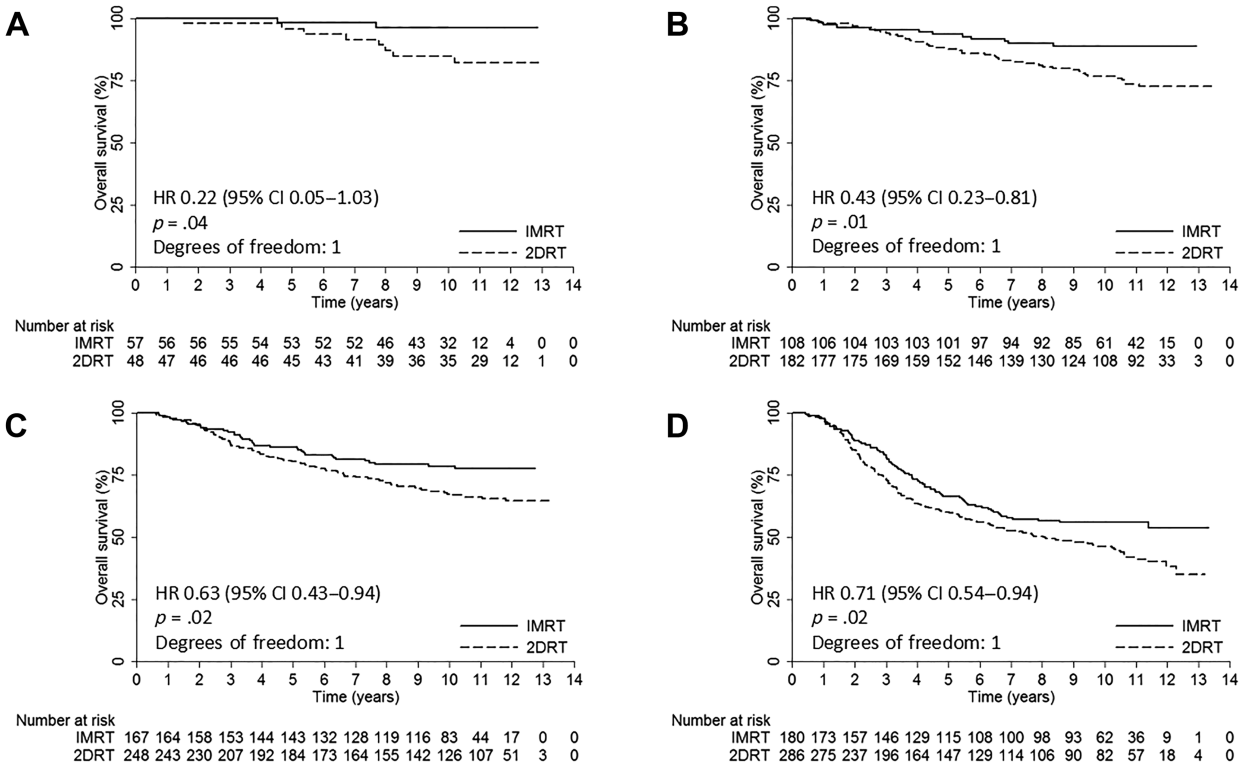

Figure 2. Kaplan-Meier overall survival curves for the IMRT group and the 2DRT group. **(A)**: Stage I. **(B)**: Stage II. **(C)**: Stage III. **(D)**: Stage IVA–B. HRs were calculated by the unadjusted Cox proportional hazards model. *P* values were calculated by the unadjusted log-rank test.

Abbreviations: 2DRT, two-dimensional radiotherapy; CI, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

time to relapse and the advance of salvage treatment, a follow-up of less than 5 years in NPC was unlikely to observe most deaths from disease progression [19]. Furthermore, a long-term follow-up is really needed to capture some unexpected adverse effects and noncancer deaths [8].

IMRT did not alter the NPC failure pattern, and distant metastasis remained the predominant mode of treatment failure. Intriguingly, newer drugs, molecular targeted agents, and immunotherapy have shown promising results of systemic control in patients with NPC or recurrent head and neck cancer by eradicating micrometastases [20–22]. Meanwhile, attaining favorable local control in patients with extensive primary tumors remains a significant clinical challenge. There is a great deal of interest at present in the use of more advanced radiotherapeutic technique, such as intensity-modulated proton therapy and heavy ion radiotherapy, to treat NPC [23, 24]. Owing to the characteristics in physics and biological effect, these advanced radiotherapeutic techniques could be expected to further improve local control in patients with extensive primary tumors without increasing toxicities.

To our knowledge, this 10-year follow-up report is the first study to confirm the ultimate therapeutic ratio of IMRT compared with 2DRT in patients with NPC. It should be noted that our study was a nonrandomized designed study because of its retrospective nature. Nevertheless, characteristics of the patients in both groups were similar, and we also attempted to reduce any potential bias by using multivariate analyses and subgroup stratification by classification and stage. In addition, the data of late toxicities were based largely on clinical observations, and regular audiometry and/or imaging were not specified during follow-up; thus, underestimation could not be excluded.

Conclusion

IMRT demonstrated an improved ultimate therapeutic ratio compared with 2DRT in patients with NPC after a 10-year follow-up, with significant improvement of L-FFS, FFS, and OS and decrease in most late toxicities and noncancer death. However, distant control remains insufficient with this treatment modality.

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Disclosures

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