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Original Article

Prognostic value of gross tumor regression and plasma Epstein Barr Virus DNA levels at the end of intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma

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ABSTRACT

Purpose: To assess gross tumor regression and plasma Epstein–Barr virus (EBV)-DNA levels at the end of intensity-modulated radiation therapy (IMRT) and its prognostic impact on patients with nasopharyngeal carcinoma (NPC).

Participants and Methods: In total, 397 patients with non-metastatic, histologically confirmed NPC were retrospectively examined. All patients underwent magnetic resonance imaging of the nasopharynx and neck, and plasma EBV DNA assays before treatment and at the end of IMRT.

Results: The estimated 5-year loco-regional, local and regional relapse-free survival rates for patients with complete response (CR) and non-CR of the total tumor, primary tumor and metastatic lymph nodes at the end of IMRT were 94.9% vs. 85.8%, 96.6% vs. 87.3%, and 98.7% vs. 89.8%, respectively ($P < 0.05$). The estimated 5-year loco-regional relapse-free survival (LRRFS) rates for patients with persistent tumor with and without boost irradiation were 95.3% vs. 83%, respectively ($P = 0.034$). The estimated 5-year overall survival (OS), failure-free survival (FFS) and distant metastasis-free survival (DMFS) rates for patients with negative and positive plasma EBV DNA at the end of IMRT were 83.1% vs. 50.3%, 81.5% vs. 49.3%, and 87.6% vs. 61.5%, respectively ($P < 0.001$). Multivariate analyses indicated that regression of the total tumor and boost irradiation was an independent predictor of LRRFS, and plasma EBV DNA levels were independent predictors of OS, FFS and DMFS.

Conclusions: Gross tumor regression and plasma EBV DNA levels at the end of IMRT served as predictors of poor prognosis for patients with NPC. The patients with persistent tumor and/or positive plasma EBV DNA might require timely strengthening treatment.

Radical radiotherapy (RT) is the first treatment option for non-metastatic nasopharyngeal carcinoma (NPC). Intensity-modulated radiation therapy (IMRT) was a milestone development in RT technology, as IMRT can provide a high conformal radiation dose to the tumor target area while effectively decreasing the dose to the surrounding normal tissues. IMRT, instead of 2-dimensional RT (2-DRT) and 3-dimensional conformal RT (3-DCRT), is currently more commonly used to treat NPC, due to the associated better tumor control and lower RT-related toxicities [1–5]. The 5-year overall survival (OS), 5-year local relapse-free survival (LRFS), 5-year regional relapse-free survival (RRFS), and 5-year distant metastasis-free survival (DMFS) rates of patients with NPC treated with IMRT ranged from 74% to 84%, 83% to 95%, 91% to 97%, and 83.3% to 85.6%, respectively [6–10].

Both loco-regional relapse and distant metastasis are the main reasons of treatment failure in patients with NPC [6–10]. Due to the poor survival of patients with loco-regional relapse and distant metastasis, some effective therapy should be done to prevent treatment failure [11–13]. Nowadays, the treatment strategy of NPC

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patients is mainly based on clinical tumor stage and plasma Epstein–Barr virus (EBV) DNA levels before treatment [14]. However, little is timely done to patients with poor treatment effect at the end of RT instead of observation in follow-up.

Only few studies have assessed the relationship between tumor regression and survival outcome in patients with NPC. The previous study found that the regression speed of the primary tumor (PT) after RT was an independent prognostic factor of OS, failure-free survival (FFS), and DMFS in NPC patients. However, that study had several limitations. First, it only evaluated the prognostic factor of tumor regression for the PT, and did not include metastatic neck lymph nodes. Second, 2-DRT and 3-DCRT were used instead of IMRT due to limited medical resources. Third, all patients were treated with RT alone or with concurrent chemoradiotherapy, and did not receive neoadjuvant chemotherapy or adjuvant chemotherapy [15].

Besides gross tumor regression, plasma EBV DNA levels are monitoring indexes during NPC treatment in the clinic. There have been a number of studies confirming that plasma EBV DNA levels are important prognostic factors before treatment, and it is also an indicator warning tumor relapse in follow-up of NPC patients [16–18]. However, it is a lack of studies on the influences of plasma EBV DNA levels at the end of IMRT on survival of NPC patients.

The prognostic impact of gross tumor regression and plasma EBV DNA levels at the end of IMRT on long-term survival in NPC patients remains unknown. If patients with poor tumor regression and positive plasma EBV DNA at the end of IMRT are at high risk of treatment failure, these patients may require timely strengthening treatment. In the present retrospective study, we aimed to assess gross tumor regression and plasma EBV DNA levels at the end of IMRT and evaluate the prognostic significance in NPC patients.

Participants and methods

Patient characteristics

The Institutional Review Board of the study institute approved this retrospective study. Informed consent was obtained from all the patients. The key raw data have been uploaded onto the Research Data Deposit public platform (RDD), with the approval number of RDDA2018000862. Between June 2010 and March 2014, 397 consecutive patients with newly diagnosed, histologically proven, non-metastatic NPC treated with IMRT at the study institute were included. All patients had the non-keratinizing pathological type, and included 298 men and 99 women (male:female ratio, 3:1), with a median age of 47 years (range, 17–80 years).

Pretreatment examination included medical history taking, physical examination, hematology and biochemistry profiles, plasma EBV DNA copy number, nasal endoscopy and biopsy, chest radiography, abdominal ultrasound, bone scan, and magnetic resonance imaging (MRI) of the nasopharynx and neck. All the patients were then restaged according to the 8th edition of the American Joint Commission on Cancer staging system (AJCC) [19]. The stage distribution was as follows: 104/397 (26.2%) with T1, 59 (14.9%) with T2, 137 (34.5%) with T3, and 97 (24.4%) with T4; 47 (11.8%) with N0, 225 (56.7%) with N1, 90 (22.7%) with N2, and 35 (8.8%) with N3; and 21 (5.3%) with stage I, 96 (24.2%) with stage II, 154 (38.8%) with stage III, and 126 (31.7%) with stage IVa.

Treatment

All patients were treated using IMRT. The target volumes were delineated according to the RTOG IMRT protocols as described previously [20–22]. Boost irradiation was administered, if necessary, to the PT or MLNs with obvious residual disease at the end of RT, and did not exceed 16 Gy. In total, 46 patients (46/397, 11.6%) received boost irradiation, including 33 patients treated with brachytherapy, 12 patients treated with 2D-RT, and 1 patient treated with IMRT.

Chemotherapy was given based on the principles of treatment for NPC patients at the study institute [22]. In total, 92.1% (258/280) patients with stage III-IVa NPC received chemotherapy: 162 received induction chemotherapy + concurrent chemotherapy, 66 received concurrent chemotherapy, 29 received induction chemotherapy, and only 1 patient received adjuvant chemotherapy. In the event of documented relapse or persistent disease, salvage treatments such as RT, surgery, or chemotherapy were administered when appropriate.

Image assessment

All patients underwent MRI of the nasopharynx and neck before the initiation of treatment and at the end of RT. The second MRI examination would be scheduled on the day of the last RT fraction, or 1–2 days before or after the last fraction. Two radiologists, with certifications of professional diagnostic imaging and with clinical focus on head and neck cancer (>10 years' experience), evaluated the magnetic resonance images separately. Any discord in the evaluation was resolved by consensus every 2 weeks. The metastatic lymph nodes (MLNs) were diagnosed based on the criteria recommended by Van et al. and Mao et al. [23–24]. Diagnostic criteria of tumor residue were based on the criteria recommended by Lv et al. [25]. The maximum tumor diameter (MTD) of the PT, metastatic retropharyngeal lymph nodes (RLNs), and metastatic neck lymph nodes (NLNs) was measured separately. The RLNs would be considered as part of the PT if it was difficult to distinguish between them. The method applied for measuring MTD was based on the previous study [15]. The total MTD was estimated as the sum of the MTD of the PT and MLNs. Tumor regression was evaluated based on the change in the total MTD before treatment and at the end of RT. Tumor regression was divided into 4 levels: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors (RECIST) [26].

Evaluation of plasma EBV DNA levels

The plasma EBV DNA levels were measured using real-time quantitative polymerase chain reaction (PCR) before and after treatment as described previously [27]. Plasma DNA was extracted and RT-PCR was performed basing on the EBV PCR fluorescence quantitative diagnostic kit (Da-AN Genetic Diagnostic Center, Sun Yat-Sen University). The assay was developed for detection of plasma EBV DNA and targeted the BamHI-W region of EBV genome. At the study institute, plasma EBV DNA copy number <1000 copies/ml was defined as negative, ≥1000 copies/ml as positive.

Follow-up

Patients were assessed every 3 months during first 2 years after RT, and every 6 months thereafter. The median follow-up duration of the entire group was 66 months (range, 5–96 months).

OS was measured from the first day of treatment to the date of death from any cause. FFS was defined as the first occurrence of tumor failure at any site. LRFS, RRFS, and DMFS were recorded as the first local, regional, or remote failure, respectively. Distant metastases were diagnosed based on the clinical symptoms, physical examination findings, and results of imaging methods such as radiography, abdominal sonography, bone scan, computed tomography (CT), MRI, and positron emission tomography-computed

tomography (PET-CT). Locoregional recurrence was diagnosed based on fiberoptic endoscopy, biopsy, MRI, and PET-CT.

Statistical analysis

All analyses were performed using SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA). Actuarial rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses with the Cox proportional hazards model were used to identify significant independent prognostic factors by backward elimination. The parameters included in the Cox proportional hazards model were: age (≤45 years vs. >45 years), sex (male vs. female), chemotherapy (yes vs. no), boost irradiation (yes vs. no), T category (T1-2 vs. T3-4), N category (N0-1 vs. N2-3). The criterion for statistical significance was set at $\alpha = 0.05$; *P*-values were based on two-sided tests.

Results

Gross tumor regression and plasma EBV DNA at the end of IMRT

At the end of IMRT, among 397 patients, regression of the total tumor was noted in 191 (48.1%) patients with CR, 194 (48.9%) with PR, 11 (2.8%) with SD, and 1 (0.3%) with PD. Among 397 patients, regression of the PT was noted in 250 (63%) patients with CR, 119 (30%) with PR, 27 (6.8%) with SD, and 1 (0.3%) with PD. Among 350 patients, regression of MLNs, including the RLN and NLN, was noted in 241 (68.9%) patients with CR, 96 (27.4%) with PR, 11 (3.1%) with SD, and 2 (0.6%) with PD.

Among 397 patients, before treatment, positive plasma EBV DNA was noted in 136 (34.3%) patients. At the end of IMRT, positive plasma EBV DNA was noted in 34 (8.6%) patients. The positive plasma EBV DNA rate in patients with non-CR of the total tumor was not significantly higher than that in patients with CR at the end of IMRT (9.7% vs. 7.3%, $P = 0.397$).

Prognostic value of regression of the total tumor at the end of IMRT

Based on the regression of the total tumor at the end of IMRT, 397 patients were divided into 2 groups: 191 patients with CR and 206 patients with non-CR. The estimated 5-year OS rates for patients with CR and non-CR were significantly different (86% vs. 75.1%, hazard ratio [HR]: 1.756, 95% confidence interval [CI]: 1.140–2.704, $P = 0.009$; Fig. 1A). The estimated 5-year FFS rates were 83.3% and 76.5%, respectively (HR: 1.618, 95% CI: 1.043–2.510, $P = 0.030$; Fig. 1B); similarly, the 5-year LRRFS rates were 94.9% and 85.8%, respectively (HR: 2.841; 95% CI: 1.384–5.831, $P = 0.003$; Fig. 1C), whereas the 5-year DMFS rates were not significantly different (84.9% vs. 85.8%, $P = 0.802$). On multivariate analyses, regression of the total tumor at the end of IMRT was found to be an independent prognostic factor of LRRFS (HR = 3.446, 95% CI: 1.699–7.117, $P = 0.001$; Table 1).

Prognostic value of regression of the primary tumor at the end of IMRT

Based on regression of the PT at the end of IMRT, 397 patients were divided into 2 groups: 250 patients with CR and 147 patients with non-CR. The estimated 5-year OS rates for patients with CR and non-CR were 85.6% and 71.5%, respectively (HR: 1.926, 95% CI: 1.273–2.912, $P = 0.002$; Fig. 2A). The estimated 5-year LRFS rates were also significantly different (96.6% vs. 87.3%, HR: 3.156, 95% CI: 1.444–6.896, $P = 0.002$; Fig. 2B), whereas the 5-year FFS rates were approximately statistically different (81.9% vs. 73.1%, HR: 1.495, 95% CI: 0.975–2.293, $P = 0.063$; Fig. 2C). However, the 5-year DMFS rates were not significantly different (86% vs. 84.2%; $P = 0.621$). On multivariate analyses, regression of the PT at the end of IMRT was found to be an independent prognostic factor of OS (HR = 1.686, 95% CI: 1.095–2.597, $P = 0.018$) and LRFS (HR = 2.941, 95% CI: 1.294–6.687, $P = 0.010$; Supplementary Table 1).

Prognostic value of regression of metastatic lymph nodes at the end of IMRT

Based on the regression of MLNs at the end of IMRT, 350 patients were divided into 2 groups: 241 patients with CR and 109 patients with non-CR. The estimated 5-year OS rates were significantly different between patients with CR and patients with non-CR (81.7% vs. 72.9%, HR: 1.649, 95% CI: 1.075–2.532, $P = 0.020$; Fig. 3A). The estimated 5-year FFS rates were significantly different (80% vs. 67.7%, HR: 1.763, 95% CI: 1.144–2.717, $P = 0.009$; Fig. 3B). The estimated 5-year RRFS rates were 98.7% and 89.8%, respectively (HR: 8.572, 95% CI: 2.391–30.732, $P < 0.001$; Fig. 3C), whereas the 5-year DMFS rates did not significantly differ (84.6% vs. 81.8%, $P = 0.526$). On multivariate analyses, regression of the MLNs at the end of IMRT was found to be an independent prognostic factor of RRFS (HR = 7.387, 95% CI:1.979–27.577, $P = 0.003$; Supplementary Table 2).

Value of boost irradiation in patients with persistent tumor at the end of IMRT

Of 206 patients with persistent tumor at the end of IMRT, 162 were not treated with boost irradiation and 44 were treated with

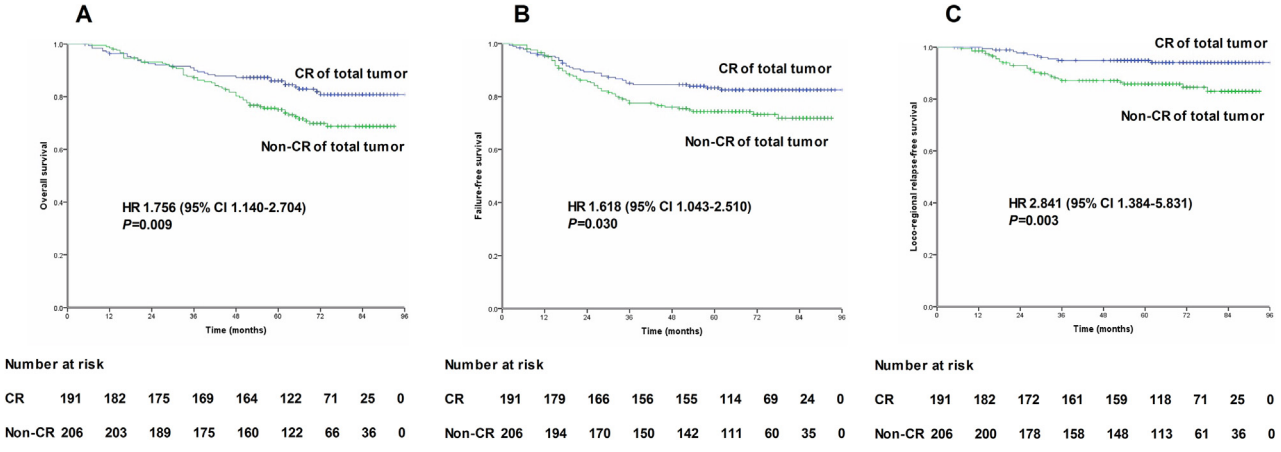

Fig. 1. Prognostic comparison of 397 patients with complete response (CR) and non-complete response (non-CR) of the total tumor at the end of intensity-modulated radiation therapy. (A) Overall survival. (B) Failure-free survival. (C) Loco-regional relapse-free survival.

Table 1
Multivariate analyses of prognostic factors in 397 nasopharyngeal carcinoma patients treated with intensity-modulated radiation therapy.

Endpoint	Variable	HR	95% CI	*P* value[†]
OS	T category[‡]	2.281	1.390–3.744	0.001
	N category[‡]	2.152	1.400–3.306	<0.001
	EBV DNA	2.321	1.314–4.098	0.004
FFS	T category[‡]	1.709	1.057–2.762	0.029
	N category[‡]	2.000	1.286–3.110	0.002
	EBV DNA	2.813	1.607–4.925	<0.001
LRRFS	Gross tumor regression	3.446	1.699–7.117	0.001
	Boost irradiation	4.278	1.018–17.970	0.047
DMFS	T category[‡]	2.130	1.134–4.000	0.019
	N category[‡]	2.434	1.406–4.213	0.001
	EBV DNA	2.831	1.473–5.439	0.002

The parameters included in the Cox proportional hazards model were: age (≤45 years vs. >45 years), sex (male vs. female), chemotherapy (yes vs. no), boost irradiation (yes vs. no), T category (T1-2 vs. T3-4), N category (N0-1 vs. N2-3), gross tumor regression of total tumor (CR vs. non-CR) and plasma EBV DNA at the end of IMRT (negative vs. positive).
[*] HR, hazard ratio; CI, confidence interval; OS, overall survival; FFS, failure-free survival; LRRFS, loco-regional relapse-free survival; DMFS, distant metastasis-free survival.
[†] *P* values were calculated using an adjusted Cox proportional-hazards model.
[‡] According to the 8th edition of the American Joint Commission on Cancer staging system.

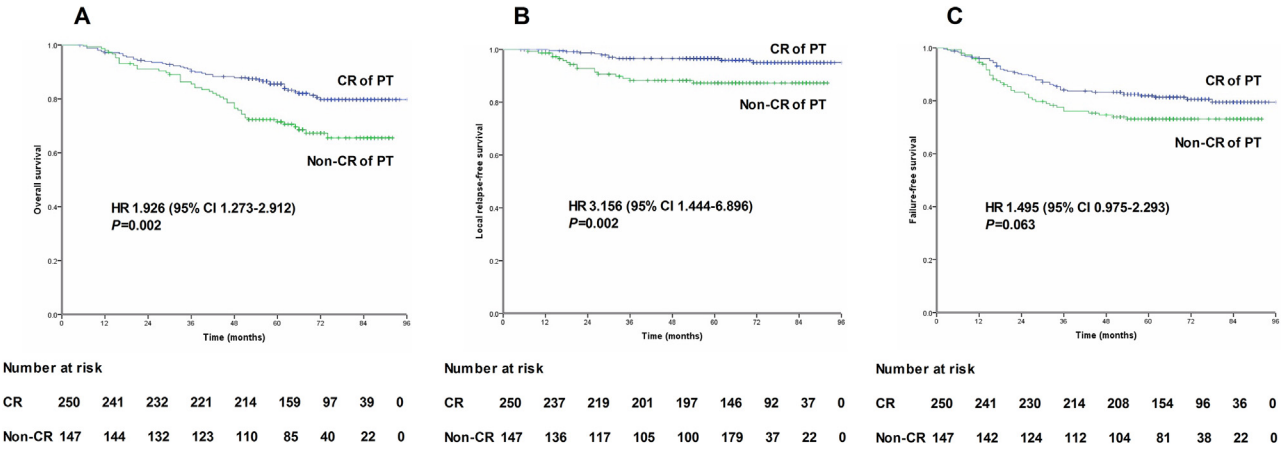

Fig. 2. Prognostic comparison of 397 patients with complete response (CR) and non-complete response (non-CR) of the primary tumor (PT) at the end of intensity-modulated radiation therapy. (A) Overall survival. (B) Local relapse-free survival. (C) Failure-free survival.

boost irradiation. The estimated 5-year LRRFS rates for patients with and without boost irradiation treatment were 95.3% and 83% (HR: 4.173, 95% CI: 0.992–17.551; $P = 0.034$; Fig. 4). The estimated 5-year OS, FFS, and DMFS rates for patients treated with boost irradiation and not treated with boost irradiation were 79.5% and 73.9% ($P = 0.129$), 84.1% and 71.6% ($P = 0.069$), and 86.4% and 85.7% ($P = 0.860$), respectively. On multivariate analyses, boost irradiation was found to be an independent prognostic factor of LRRFS (HR = 4.278, 95% CI: 1.018–17.970, $P = 0.047$; Table 1).

Prognostic value of plasma EBV DNA at the end of IMRT

Based on the plasma EBV DNA levels at the end of IMRT, 397 patients were divided into 2 groups: 363 patients with negative EBV DNA and 34 patients with positive EBV DNA. The estimated 5-year OS rates for negative patients and positive patients were 83.1% and 50.3%, respectively (HR: 3.491, 95% CI: 2.026–6.017, $P < 0.001$; Fig. 5A); similarly, the 5-year FFS rates were 81.5% and 49.3%, respectively (HR: 3.885; 95% CI: 2.275–6.636, $P < 0.001$; Fig. 5B). The estimated 5-year DMFS rates were significantly different (87.6% vs. 61.5%, HR: 4.268, 95% CI: 2.292–7.950, $P < 0.001$; Fig. 5C), whereas the 5-year LRRFS rates were not significantly different (91% vs. 79.2%, $P = 0.086$). On multivariate analyses, the plasma EBV DNA levels at the end of IMRT were found to be the independent prognostic factors of OS (HR = 2.321, 95% CI: 1.314–4.098, $P = 0.004$), FFS (HR = 2.813, 95% CI: 1.607–4.925, $P < 0.001$) and DMFS (HR = 2.831, 95% CI: 1.473–5.439, $P = 0.002$; Table 1).

Discussion

In the present study, we found that regression of the total tumor at the end of IMRT was an important prognostic factor of LRRFS in NPC patients, and also observed a relationship between regression of the PT and LRFS, and regression of the MLNs and RRFS. Boost irradiation might improve LRRFS in NPC patients with persistent tumors at the end of IMRT. Furthermore, the plasma EBV DNA levels at the end of IMRT are the independent prognostic factors of OS, FFS and DMFS in NPC patients.

In the present study, CR rates of the total tumor, PT, and MLNs at the end of IMRT were 48.1%, 63%, and 68.9%, respectively. In the previous study, only 40.4% patients exhibited CR of the PT after RT [15]. The CR rate was markedly higher in the present study, probably due to a few main reasons. First, in the present study 68.2% patients with stage III-IVa were treated with induction chemotherapy which is an effective treatment modality for patients with locoregionally advanced NPC [28,29]. Second, all patients were

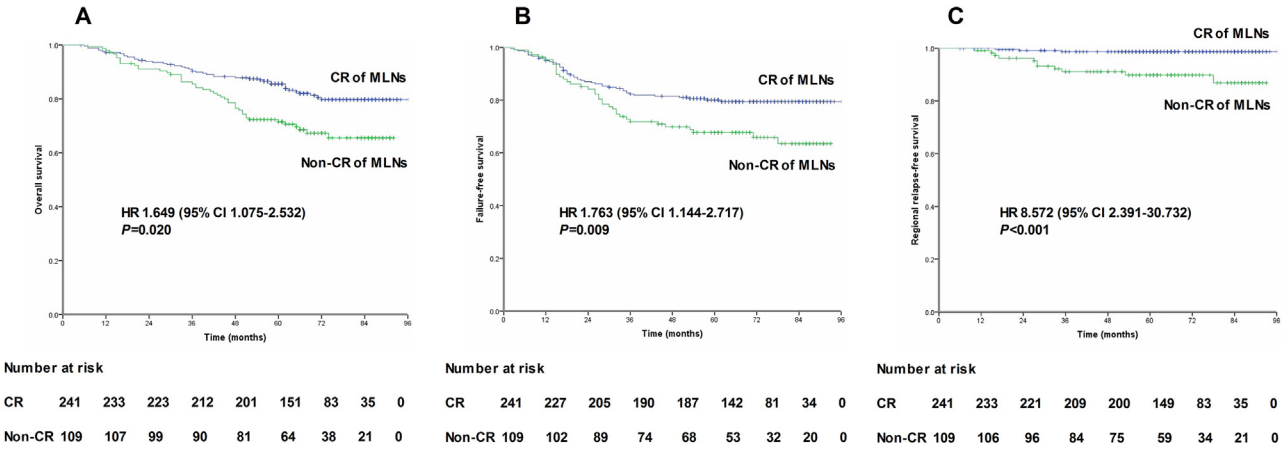

Fig. 3. Prognostic comparison of 350 patients with complete response (CR) and non-complete response (non-CR) of the metastatic lymph nodes (MLNs) at the end of intensity-modulated radiation therapy. (A) Overall survival. (B) Failure-free survival. (C) Regional relapse-free survival.

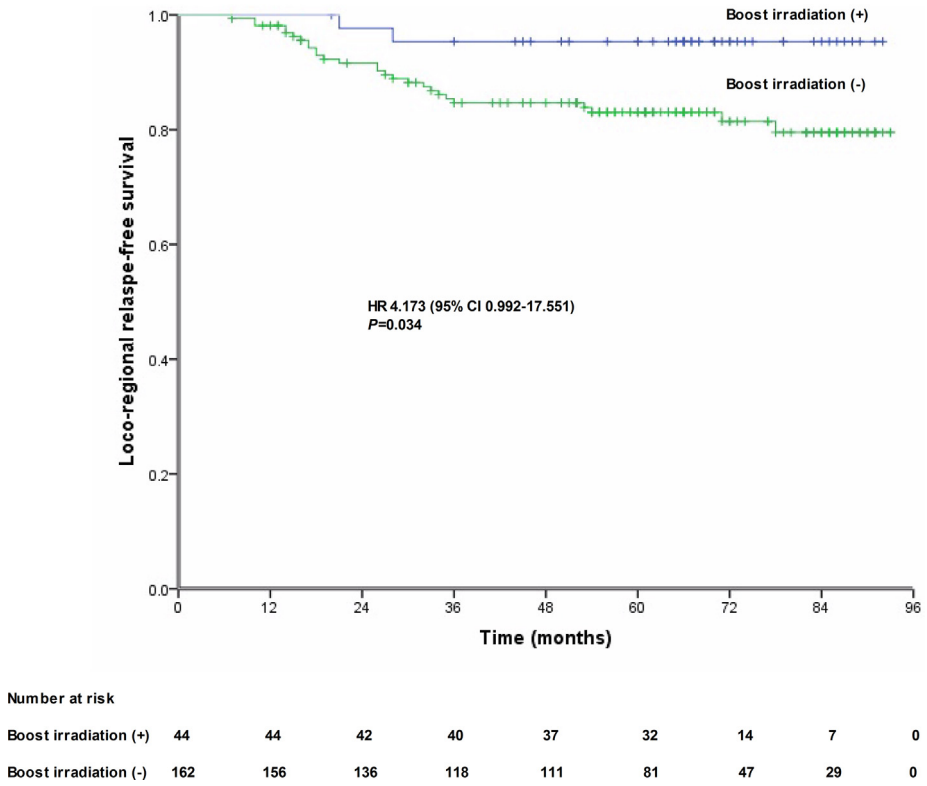

Fig. 4. Comparison of loco-regional relapse-free survival rates in 206 patients with persistent tumor at the end of intensity-modulated radiation therapy who were treated and not treated with boost irradiation.

treated with IMRT which might increase the CR rate, as compared to that with 2D-RT or 3D-CRT, due to the high and conformal radiation dose to the tumor involved in IMRT.

In this study, positive plasma EBV DNA was noted in 8.6% patients at the end of IMRT. The positive plasma EBV DNA rate in patients with residual tumor was not significantly higher than that in the other patients ($P = 0.397$). In the study by Lv et al., 6.5% patients were detected with EBV DNA after three months post-treatment. The EBV DNA was significantly associated with tumor residue after three months post-treatment [25]. The different results might due to different time points of measurement and cut-off point of EBV DNA levels.

In the present study, compared to patients with non-CR, patients with CR of the total tumor, PT, or MLNs at the end of RT exhibited better LRRFS, LRFS, and RRFS rates, respectively. Tumor regression during RT was an independent predictive factor of local control in head and neck carcinomas [30]. Furthermore, tumor regression following RT was a reliable indicator of permanent local control for oropharynx and pharyngolarynx carcinomas [31].

Among patients with persistent tumors at the end of IMRT, the estimated 5-year LRRFS rate was significantly better in those treated with boost irradiation than in those without boost irradiation treatment. Stereotactic RT boost was reportedly effective in reversing the poor prognostic influence of local persistent disease in NPC patients [32,33]. Intracavitary brachytherapy is usually administered as boost radiotherapy for superficial residual disease in NPC patients after primary external beam RT. Endoscope-guided interstitial intensity-modulated brachytherapy boost radiation

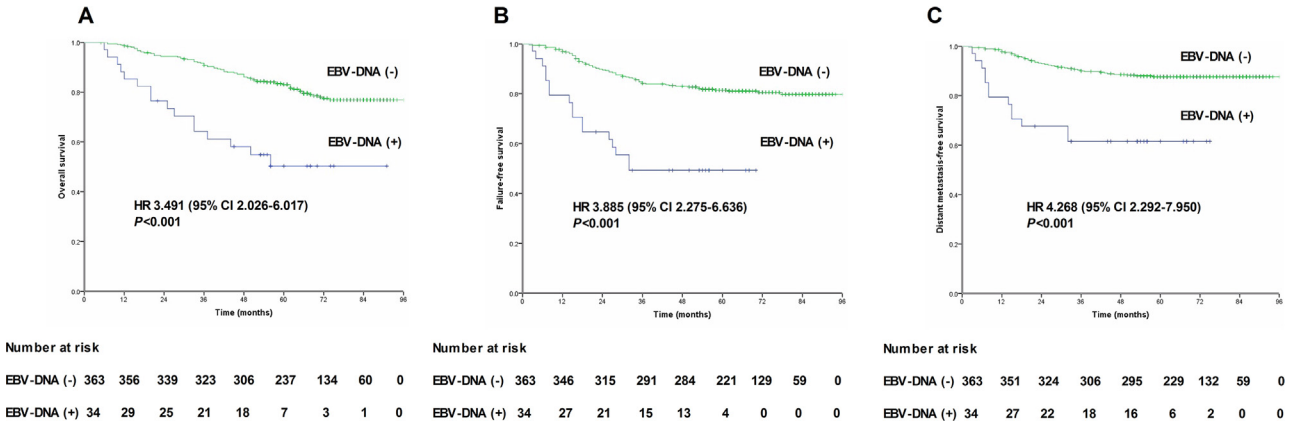

Fig. 5. Prognostic comparison of 397 patients with negative plasma EBV DNA and positive plasma EBV DNA at the end of intensity-modulated radiation therapy. (A) Overall survival. (B) Failure-free survival. (C) Distant metastasis-free survival.

might also be a promising therapeutic option for deep-seated residual NPC [34]. However, Schinagl et al. reported that, although external beam radiotherapy with endocavitary brachytherapy produces excellent rates of local control for T1-2 tumor, the high incidence of late toxicity could indicate overtreatment [35]. Due to the high risk of loco-regional relapse in patients with persistent tumor at the end of RT, additional studies are needed to explore timely and effective treatment in these patients.

In the present study, compared to patients with negative plasma EBV DNA at the end of IMRT, patients with positive plasma EBV DNA had worse OS, FFS and DMFS rates. In the study by He et al., detectable EBV DNA at the end of treatment was also associated with significantly poorer OS, DMFS, and progression-free survival (PFS). Among patients with detectable EBV DNA at the end of treatment, adjuvant therapy significantly improved OS ($P = 0.03$) and DMFS ($P = 0.04$) [36]. Adjuvant therapy might bring survival benefit to these patients with positive plasma EBV DNA at the end of RT, but it needs to be confirmed by prospective clinical trials.

The present study has certain limitations. First, as it is a retrospective study, various different chemotherapy regimens were administered, which could have affected the treatment outcome (Supplementary Material). Second, the choice of which patients should receive boost irradiation was based on the clinical experience of their doctors, and might result in some selection bias; hence, the conclusions should be confirmed in further prospective studies. Third, plasma EBV DNA copy number was not quantitatively detected when its level was <1000 copies/ml, thus the EBV PCR fluorescence quantitative diagnostic kit is needed to be improved.

Conclusions

In conclusion, gross tumor regression at the end of IMRT was an independent prognostic factor of local and/or regional tumor control in NPC patients. Boost irradiation might improve loco-regional tumor control in NPC patients with persistent tumor at the end of IMRT. The plasma EBV DNA levels at the end of IMRT were the independent prognostic factors of OS, FFS and DMFS in NPC patients. Some timely and effective strengthening treatment might be administered to patients with persistent disease and/or positive plasma EBV DNA at the end of IMRT.

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Conflict of interest statement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.010.

References

[1] Zhang MX, Li J, Shen GP, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up. Eur J Cancer 2015;51:2587–95.
[2] Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. Oral Oncol 2015;51:1041–6.
[3] Qiu WZ, Peng XS, Xia HQ, et al. A retrospective study comparing the outcomes and toxicities of intensity-modulated radiotherapy versus two-dimensional conventional radiotherapy for the treatment of children and adolescent nasopharyngeal carcinoma. Cancer Res Clin Oncol 2017;143:1563–72.
[4] Moon SH, Cho KH, Lee CG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). Strahlenther Onkol 2016;192:377–85.
[5] Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer—success and setback in the intensity-modulated radiotherapy era. Radiother Oncol 2014;110:377–84.
[6] Ou X, Zhou X, Shi Q, et al. Treatment outcomes and late toxicities of 869 patients with nasopharyngeal carcinoma treated with definitive intensity modulated radiation therapy: new insight into the value of total dose of cisplatin and radiation boost. Oncotarget 2015;6:38381–97.
[7] Setton J, Han J, Kannarunimit D, et al. Long-term patterns of relapse and survival following definitive intensity-modulated radiotherapy for non-endemic nasopharyngeal carcinoma. Oral Oncol 2016;53:67–73.
[8] Lin S, Pan J, Han L, et al. Update report of nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy and hypothesis of the optimal margin. Radiother Oncol 2014;110:385–9.
[9] Sun X, Su S, Chen C, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. Radiother Oncol 2014;110:398–403.
[10] Yi J, Huang X, Gao L, et al. Intensity-modulated radiotherapy with simultaneous integrated boost for locoregionally advanced nasopharyngeal carcinoma. Radiat Oncol 2014;9:56.
[11] Tian YM, Huang WZ, Yuan X, et al. The challenge in treating locally recurrent T3–4 nasopharyngeal carcinoma: the survival benefit and severe late toxicities of re-irradiation with intensity-modulated radiotherapy. Oncotarget 2017;8:43450–7.
[12] Ng WT, Ngan RKC, Kwong DLW, et al. Prospective, multicenter, phase 2 trial of induction chemotherapy followed by bio-chemoradiotherapy for locally advanced recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2018;100:630–8.

[13] Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2016;388:1883–92.
[14] Lin JC, Chen KY, Wang WY, et al. Detection of Epstein-Barr virus DNA in the peripheral-blood cells of patients with nasopharyngeal carcinoma: relationship to distant metastasis and survival. J Clin Oncol 2001;19:2607–15.
[15] Zhang N, Liang SB, Deng YM, et al. Primary tumor regression speed after radiotherapy and its prognostic significance in nasopharyngeal carcinoma: a retrospective study. BMC Cancer 2014;14:136.
[16] Liu LT, Tang LQ, Chen QY, et al. The prognostic value of plasma Epstein-Barr Viral DNA and tumor response to neoadjuvant chemotherapy in advanced-stage nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2015;93:862–9.
[17] Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 2004;350:2461–70.
[18] Liu TB, Zheng ZH, Pan J, et al. Prognostic role of plasma Epstein-Barr virus DNA load for nasopharyngeal carcinoma: a meta-analysis. Clin Invest Med 2017;40: E1–E12.
[19] Amin MB, Edge S, Greene F, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
[20] Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 2009;27:3684–90.
[21] Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 2012;13:172–80.
[22] Liang SB, Wang Y, Hu XF, et al. Survival and toxicities of IMRT based on the RTOG protocols in patients with nasopharyngeal carcinoma from the endemic regions of China. J Cancer 2017;8:3718–24.
[23] Van den Brekel MW, Stel HV, Castelijns JA, et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990;177:379–84.
[24] Mao YP, Liang SB, Liu LZ, et al. The N staging system in nasopharyngeal carcinoma with radiation therapy oncology group guidelines for lymph node levels based on magnetic resonance imaging. Clin Cancer Res 2008;14:7497–503.
[25] Lv JW, Zhou GQ, Li JX, et al. Magnetic resonance imaging-detected tumor residue after intensity-modulated radiation therapy and its association with post-radiation plasma epstein-barr virus deoxyribonucleic acid in nasopharyngeal carcinoma. J Cancer 2017;8:861–9.
[26] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[27] Wei W, Huang Z, Li S, et al. Pretreatment Epstein-Barr virus DNA load and cumulative cisplatin dose intensity affect long-term outcome of nasopharyngeal carcinoma treated with concurrent chemotherapy: experience of an institute in an endemic area. Oncol Res Treat 2014;37:88–95.
[28] Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016;17:1509–20.
[29] Peng H, Chen L, Zhang J, et al. Induction chemotherapy improved long-term outcomes of patients with locoregionally advanced nasopharyngeal carcinoma: a propensity matched analysis of 5-year survival outcomes in the era of intensity-modulated radiotherapy. J Cancer 2017;8:371–7.
[30] Jaulerry C, Dubray B, Brunin F, et al. Prognostic value of tumor regression during radiotherapy for head and neck cancer: a prospective study. Int J Radiat Oncol Biol Phys 1995;33:271–9.
[31] Bataini JP, Jaulerry C, Brunin F, et al. Significance and therapeutic implications of tumor regression following radiotherapy in patients treated for squamous cell carcinoma of the oropharynx and pharyngolarynx. Head Neck 1990;12:41–9.
[32] Yau TK, Sze WM, Lee WM, et al. Effectiveness of brachytherapy and fractionated stereotactic radiotherapy boost for persistent nasopharyngeal carcinoma. Head Neck 2004;26:1024–30.
[33] Hara W, Loo Jr BW, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2008;71:393–400.
[34] Wan XB, Jiang R, Xie FY, et al. Endoscope-guided interstitial intensity-modulated brachytherapy and intracavitary brachytherapy as boost radiation for primary early T stage nasopharyngeal carcinoma. PLoS One 2014;9:e90048.
[35] Schinagl DA, Marres HA, Kappelle AC, et al. External beam radiotherapy with endocavitary boost for nasopharyngeal cancer: treatment results and late toxicity after extended follow-up. Int J Radiat Oncol Biol Phys 2010;78:689–95.
[36] He SS, Wang Y, Bao Y, et al. Dynamic changes in plasma Epstein-Barr virus DNA load during treatment have prognosticvalue in nasopharyngeal carcinoma: a retrospective study. Cancer Med 2018;7:1110–7.