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ORIGINAL ARTICLE

Predictive value of tumor volume reduction rates before and after induction chemotherapy in determining the radiosensitivity and prognosis of locally advanced nasopharyngeal carcinomas

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Abstract

Objective This study investigated the predictive value of tumor volume reduction rates (TVRRs) before and after induction chemotherapy in determining the radiosensitivity and prognosis of patients with locally advanced nasopharyngeal carcinomas (NPCs).

Methods The clinical data of 172 patients with locally advanced primary NPCs who were treated from January 2009 to December 2012 were collected. Tumor regression was evaluated based on the results of the computed tomography scan or magnetic resonance imaging studies. Data about the tumor diameters before and after induction chemotherapy and after radiotherapy as well as the survival times of the patients were obtained.

Results All 172 patients had NPCs. After radiotherapy, the TVRR in patients without residual tumor cells was higher than that in patients with residual tumor cells after induction chemotherapy (median values: 47.7% and 15.1%, respectively), and the 5-year survival rates were 80.3% and 45.6%, respectively. Neck lymph node metastasis was observed in 161 of 172 patients, and the TVRRs were similar (median values: 46.8% in 161 patients without residual tumor cells and 11.1% in 161 patients with residual tumor cells). The 5-year survival rate of the 161 patients without residual tumor cells was 84.5%, and that of patients with residual tumor cells was 37.3%. As shown by the receiver operating characteristic (ROC) curve, the area under the curve (AUC) of the ROC curve for TVRRs in patients with primary NPCs but without residual tumors was 0.851, whereas that for TVRRs in patients with neck lymph node metastasis but without residual tumors was 0.784. This result indicates that TVRR has a high diagnostic performance. The univariate Cox regression analysis showed that clinical stage, TVRR in primary NPCs, neck lymph node metastatic lesions before and after induction chemotherapy, presence or absence of residual tumor cells in primary NPCs, and neck lymph node metastatic lesions after radiotherapy were significantly correlated to overall survival (OS). Results of the multivariate Cox regression analysis showed that clinical stage and presence or absence of residual tumor cells in the lymph nodes after radiotherapy were the independent prognostic factors of OS.

Conclusion The TVRR after induction chemotherapy may be an effective predictive indicator of the treatment efficacy of radiotherapy in patients with NPC.

Key words: nasopharyngeal carcinomas; induction chemotherapy; radiosensitivity; prognosis

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The prevalence rate of nasopharyngeal carcinomas (NPCs) is extremely high in southern China. Considering the anatomical position of the nasopharynx and the different clinical symptoms of NPCs, these carcinomas are usually not diagnosed until they are at a locally advanced stage. Radiotherapy is the first choice in the treatment of NPCs. Although the efficacy of radiotherapy is high, local recurrence and distant metastasis commonly occur [1]. The prognosis of patients with NPC recurrence or distant metastasis after radiotherapy is poor, and the 5-year survival rate of patients with local recurrence is only 33% [2]. The average survival time of patients with distant metastasis is 22 months [3]. Therefore, to improve the prognosis of patients with NPC, the radiosensitivity of NPCs must be predicted, and a reliable predictive indicator should be established to guide clinical treatment.

Induction chemotherapy can reduce tumor burden, which results in local control, helps improve blood supply and radiosensitivity, and reduces the risk of subclinical metastasis. However, an ineffective induction chemotherapy delays radiotherapy, causes accelerated re-proliferation of tumor cells, and reduces local control rates. Furthermore, it causes tumor cells to be insensitive to radiotherapy transfer. Therefore, the efficacy of induction chemotherapy determines the efficacy of radiotherapy. Research about the potential ability of induction chemotherapy in predicting the efficacy of radiotherapy is limited. In our previous study, we found that changes in plasma Epstein–Barr virus (EBV) DNA levels before and after induction chemotherapy helped predict tumor volume regression after radiotherapy, although the predictive value of plasma EBV DNA levels was lower than that of imaging data [4]. Therefore, this study aimed to validate the potential ability of TVRRs before and after induction chemotherapy in predicting tumor regression and survival rates after radiotherapy.

Materials and methods

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with a pathologically confirmed NPC; (2) those with locally advanced stage III/IVA NPC without distant metastasis according to the Chinese 2008 staging system; (3) those who underwent examination of the nasopharynx via computed tomography (CT) scan or magnetic resonance imaging (MRI) before treatment, after induction chemotherapy, and after radiotherapy, electronic nasopharyngoscopy, chest CT scan, or chest radiography in addition to upper abdominal CT scan or abdominal B ultrasonography and whole-body bone scan examinations; (4) those treated with radiotherapy for the first time; (5) those with KPS ≥ 80; and (6) those with contraindications for radiotherapy treatment, which include infections, severe anemia, pulmonary tuberculosis, heart disease, kidney disease, and other comorbidities. Meanwhile, the exclusion criterion included patients who did not undergo radical radiotherapy treatment.

Clinical data of the participants

A total of 172 patients with primary NPCs who were treated in the Department of Oncology, Third Affiliated Hospital of the Third Military Medical University from January 2009 to December 2012 were included. All the patients had a pathological diagnosis of NPCs prior to treatment and underwent physical examination, complete blood count examination, liver and kidney function examination, chest radiography, abdominal B ultrasonography, head and neck CT/MRI, and whole-body bone scan. Table 1 shows the summary of the baseline information of the patients.

Treatment

Induction chemotherapy

The patients received docetaxel plus paclitaxel (TP)-or docetaxel, paclitaxel, fluorouracil (TPF)-based induction chemotherapy. The TP regimen consisted of 75 mg/m^2 of docetaxel or 135 mg/m^2 of paclitaxel on day 1 plus 80 mg/m^2 of nedaplatin on day 1. The TPF regimen involved 120 h of continuous intravenous infusion of 60 mg/m^2 of docetaxel or 135 mg/m^2 of paclitaxel on day 1 plus 80 mg/m^2 of nedaplatin on day 1 plus fluorouracil 450–550 mg/m^2 on days 1–5. Each cycle was completed within 3 weeks, and each patient received chemotherapy treatment in two cycles.

Concurrent chemotherapy during radiotherapy

The patients received 2–3 cycles of 80 mg/m^2 of nedaplatin every 3 weeks or a total of 6 cycles of 40 mg/m^2 of nedaplatin weekly.

Radiotherapy

All patients received intensity-modulated radiation therapy using a 6-MV linear accelerator (Elekta, Stockholm, Sweden) after 3–4 weeks after the completion of induction chemotherapy. A large-aperture 16-row spiral CT scanning was used after fixation with low-temperature thermoplastic film covering the head, neck, and shoulders. The treatment target was outlined based on pretreatment MRI results and the International Commission on Radiation Units and Measurements (ICRU) guidelines (reports 50 and 62). The high-risk clinical target volume (CTV1) comprised GTVnx and GTVnd with a margin of 5–10 mm, which include the whole nasopharynx, inferior two-thirds of the sphenoid sinus, the anterior third of the clivus, pterygoid fossae, posterior third of nasal cavity and maxillary sinuses, retropharyngeal nodes, parapharyngeal space, and the drainage of the upper neck. The total dose delivered to CTV1 was 60 Gy. CTV2 comprised of CTV1 with

a margin of 3–5 mm as well as the lower neck and the supraclavicular lymphatic drainage region. PTV included CTV with a margin of 3–5 mm. The prescription dose was set as follows: GTVnx PTV: 70–72.6 Gy, GTVnd PTV: 66 Gy, CTV1 PTV: 60 Gy, and CTV2 PTV: 54 Gy. The total dose of GTVnx PTV, GTVnd PTV, CTV1 PTV, and CTV2 PTV was delivered within 33 fractions. The dose for critical organs, including the brain stem, spinal cord, optic nerve, optic chiasm, temporal lobe, eyeball, lens, mandible, temporomandibular joint, parotid gland, submandibular gland, and thyroid, was in accordance with the RTOG-0615 protocol. The maximum dose of each organ at risk was below its tolerance limit. Based on the gross target volume of the primary tumor (GTVnx), a single dose of 2.12–2.2 Gy was administered, resulting in a total dose of 70–72.6 Gy. Based on the gross target volume of the metastatic lymph nodes (GTVnd), a single dose of 2.00 Gy was administered, and the total dose was 66 Gy. The maximum dose for critical organs was determined according to the RTOG-0615 protocol.

Measurement of tumor volume

Once the delineation of the rational target volume was finished, the GTVnx and GTVnd and gross tumor volume (GTV) were automatically calculated using the Elekta TPS treatment planning system (TPS). Residual lymph nodes after treatment were defined as follows: enhanced MRI results showing that the smallest diameter of the lymph nodes was > 1 cm on the maximum cross-sectional image, and enhanced scan showing obvious enhancement of lymph nodes or extracapsular invasion of lymph nodes.

Evaluation of short-term efficacy

The treatment efficacy was evaluated according to the 2009 RECIST (version l.1) 3–4 weeks after induction chemotherapy and 1 month after radiotherapy. Efficacy was defined as follows: a complete response, defined as disappearance of all target lesions; a partial response (PR), defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions; progressive disease, defined as at least a 20% increase in the sum of the LD of the target lesions or the appearance of one or more new lesions; and stable disease, defined as neither enough shrinkage of the lesion to qualify for PR nor enough increase in the size of the lesion to qualify for progressive disease.

Follow-up

After 5 years post-treatment, the patients were re-examined every 3 months. After 1-year post-treatment, they were re-examined every 6 months. In the re-examination, chest radiography, abdominal color ultrasonography, nasopharyngeal MRI, and nasopharyngoscopy were performed. Brain MRI and whole-body bone ECT scan were performed in patients with clinical symptoms. The follow-up was conducted via telephone for a maximum of 102 months. For patients who were lost to follow-up, the results of the last department visits for outpatients were used. The follow-up for all patients lasted at least 5 years. The median follow-up was 61 (range: 6–101) months.

Statistical analysis

The Kruskal–Wallis test was performed to compare the TVRRs of the patient groups with and without residual tumor cells before and after induction chemotherapy. The Cox regression model was used to analyze different clinical pathological characteristics, relationships between TVRRs and presence or absence of residual tumor cells after radiotherapy as well as OS, and independent prognostic factors of OS. All statistical analyses were performed using the Statistical Package for the Social Sciences software version 20.0 (IBM, New York), and a P value < 0.05 was considered statistically significant.

Results

Correlation between TVRRs before and after induction chemotherapy and residual tumor cells after radiotherapy

Nasopharyngeal lesions were noted in 172 patients. Neck lymph node metastasis was observed in 161 cases (Table 1). The values of the primary tumor volume (GTV) before and after induction chemotherapy were 2.8 (interquartile range [IQR]: 2.0–3.6) and 2.0 (IQR: 1.0–3.0), respectively. The values of the neck lymph node metastatic lesions (GTV) before and after induction chemotherapy were 4.0 (IQR: 2.5–6.0) and 2.8 (IQR: 1.2–4.0), respectively. In the patient group with primary NPCs without residual tumor cells after radiotherapy, the median TVRR after induction chemotherapy was 47.7% (range: 0.0%–100%), which was significantly higher than that of the patient group with residual tumor cells (median: 15.1%; range: –15.4%–87.0%, $P < 0.001$). The results for neck lymph node metastatic lesions were similar. The TVRRs (median: 46.8%; range: 0.0%–100%) of the patient group without residual tumor cells were significantly higher than those of the patient group with residual tumor cells (median: 11.1%; range: –20.0%–70.0%, $P < 0.001$) (Fig. 1).

ROC curve analyses validated the value of TVRRs after induction chemotherapy in predicting a complete response in patients with residual tumors after radiotherapy

As patients sensitive to induction chemotherapy were also sensitive to radiotherapy, the ability of TVRRs postinduction chemotherapy in predicting the absence of residual tumor cells after radiotherapy was identified via

Table 1 Baseline characteristic of the whole population

Characteristics	*n*	%
Sex		
Female	52	30.4
Male	119	69.6
T		
T1	11	6.4
T2	47	27.3
T3	62	36.0
T4	52	30.2
N		
N0	11	6.4
N1	37	21.5
N2	108	62.8
N3	16	9.3
Stage		
III	108	62.8
IV	64	37.2
Residual tumor of primary lesion		
Residual	44	25.6
Non-Residual	128	74.4
Residual tumor of node lesion		
Residual	47	27.3
Non-Residual	125	72.7
Response of primary lesion		
CR	24	14.1
PR	83	48.8
SD	63	37.1
PD	0	0.0
Response of node lesion		
CR	10	6.2
PR	94	58.4
SD	56	34.8
PD	1	0.6
ORR of primary lesion		
SD + PD	63	37.1
CR + PR	107	62.9
ORR of node lesion		
SD + PD	57	35.4
CR + PR	104	64.6
TVRR of primary lesions (median,range)		
0.410 (–0.154–1.000)		
TVRR of node lesions (median,range)		
0.396 (–0.200–1.000)		

TVRR: tumor volume reduction rates; ORR: objective response; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease

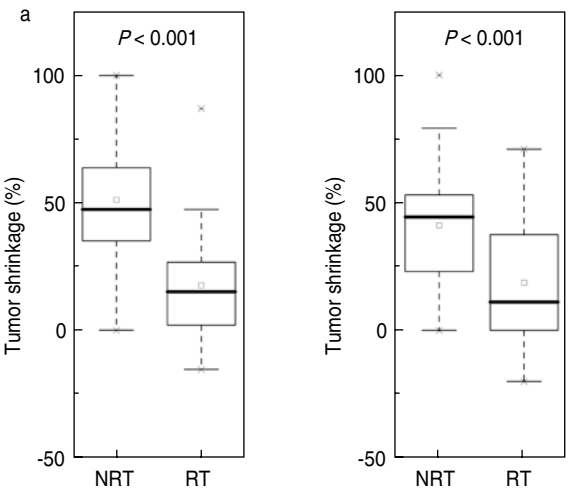

Fig. 1 Boxplot showing that patients without residual tumor had a significantly higher tumor shrinkage than those with residual tumor. (a) Nasopharyngeal primary lesion; (b) Nodal metastatic lesion. NRT: non-residual tumor; RT: residual tumor

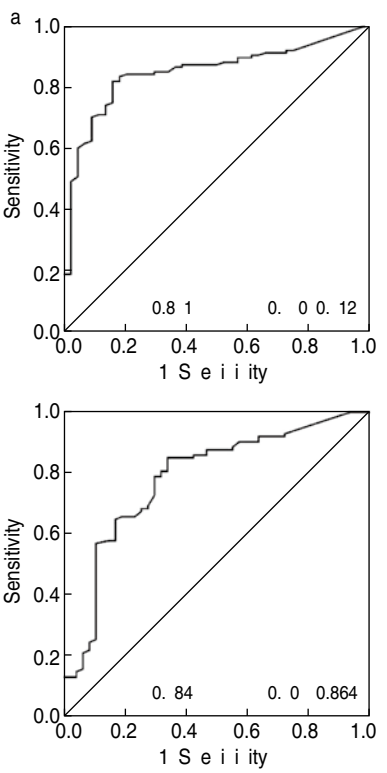

Fig. 2 Receiver operating characteristic curves illustrating the efficacy of tumor shrinkage to identify patients without tumor residual after radiation from other patients. (a) Nasopharyngeal primary lesion; (b) Nodal metastatic lesion

analysis of the ROC curve. As shown in Fig. 2, the AUC of the ROC curve for TVRRs in patients with primary NPCs but without residual tumors was 0.851 (95% confidence interval [CI]: 0.790–0.912). Moreover, the AUC of the ROC curve for TVRRs in patients with neck lymph node metastasis but without residual tumors was 0.784 (95% CI: 0.703–0.864). These results indicate that TVRRs have a high diagnostic performance. A cut-off value of 0.297 for TVRR was selected according to the maximum of Youden's statistic, which showed a specificity of 84.1%

and sensitivity of 82.0% for predicting the absence of residual primary tumors. Meanwhile, with a cut-off value of 0.1833 based on the Jorden's statistic, the specificity and sensitivity for predicting the absence of residual neck lymph node tumors was 66.0% and 85.1%, respectively.

Influence of TVRRs before and after induction chemotherapy and residual tumor cells after radiotherapy on OS

In the univariate Cox regression analysis, clinical stages, TVRRs of primary NPCs, neck lymph node metastatic lesions before and after induction chemotherapy, presence or absence of residual tumor cells in primary nasopharyngeal lesions, and neck lymph node metastatic lesions after radiotherapy were correlated to OS. The median OS of the patient group with residual tumor cells detected in primary NPCs after radiotherapy was 50.67 months (95% CI: 19.03–82.30), and the 5-year survival rate was 45.6%. The patient group without residual tumor cells did not reach the median OS due to an outstanding prognosis, and the 5-year survival rate was 80.3% (log-rank test, $P < 0.001$) (Fig. 3a). The median OS of the patient group with residual tumor cells and neck lymph node metastatic lesions was 39.6 months (95% CI: 25.72–53.48), and the 5-year survival rate was 37.3%. The patient group without residual tumor cells did not reach the median OS, and the 5-year survival rate was 84.5% (log-rank test, $P < 0.001$) (Fig. 3b). Sex, age, and TN staging were used in the multivariate Cox regression analysis. Results showed that the clinical stage and presence or absence of residual tumor cells in the lymph nodes after radiotherapy were the independent prognostic factors of OS. The risk of mortality in patients with stage IV disease increased by 97.5% compared with that of patients with stage III disease. After radiotherapy, the risk of mortality in patients without residual tumor cells and neck lymph node metastasis decreased by 67% compared with that of patients with residual tumor cells (Table 2).

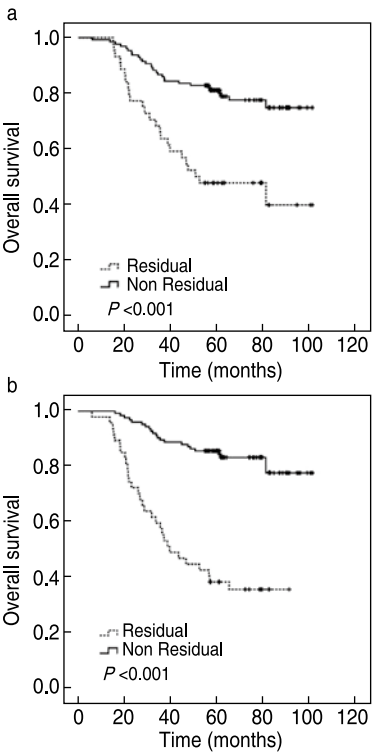

Fig. 3 Kaplan–Meier estimates of overall survival. Patients without any tumor residuals after radiotherapy exhibited a significantly longer overall survival than those with tumor residuals. (a) Nasopharyngeal primary lesion; (b) Nodal metastatic lesion

Subgroups analysis for evaluating the potential influence of T and N stage on the prognostic value of TVRRs in identifying OS

Except for the presence or absence of residual tumor cells in the lymph nodes, all other important prognostic factors observed in the whole population did not show a significant association with OS in the T1–T2 subset. In contrast, in the T3-T4 subgroup, the TVRRs of primary NPCs, neck lymph node metastatic lesions, presence or

Table 2 Results of Cox regression analysis

Factors	Univariable Cox		Multivatiable Cox	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (Male vs. Female)	1.036 (0.269–1.888)	0.908	1.047 (0.553–1.982)	0.888
Age†	0.993 (0.968–1.018)	0.572	0.978 (0.949–1.007)	0.137
T (T3–T4 vs T1–T2)	1.856 (0.973–3.540)	0.060	1.231 (0.582–2.604)	0.587
N (N1–N3 vs. N0)	22.75 (0.252–2051)	0.174	a	a
Stage (IV vs. III)	2.307 (1.337–3.983)	0.003	1.975 (1.091–3.574)	0.025
Shrinkage of primary lesion†	0.145 (0.051–0.413)	<0.001	0.618 (0.185–2.066)	0.434
Shrinkage of nodal lesion†	0.098 (0.031–0.315)	<0.001	0.480 (0.131–1.757)	0.268
Residual of primary lesion (No vs. Yes)	0.312 (0.181–0.540)	<0.001	0.577 (0.302–1.104)	0.097
Residual of nodal lesion (No vs. Yes)	0.186 (0.107–0.323)	<0.001	0.326 (0.171–0.621)	0.001

†as continuous covariates entered into equations
a: Degree of freedom reduced because of constant or linearly dependent covariates

Table 3 Univariate Cox regression in subgroup

	T1–T2		T3–T4		$P_{interaction}$
	HR (95% CI)	*P*	HR (95% CI)	*P*	
Shrinkage of primary lesion†	0.595 (0.093–3.802)	0.584	1.047 (0.553–1.982)	0.888	0.100
Shrinkage of nodal lesion†	0.111 (0.007–1.696)	0.114	0.978 (0.949–1.007)	0.137	0.895
Residual of primary lesion (No vs Yes)	1.024 (0.132–7.959)	0.982	1.231 (0.582–2.604)	0.587	0.227
Residual of nodal lesion (No vs Yes)	0.309 (0.100–0.961)	0.043	a	a	0.336
	N0–N1		N2–N3		$P_{interaction}$
	HR (95% CI)	*P*	HR (95% CI)	*P*	
Shrinkage of primary lesion†	0.022 (0.002–0.329)	0.006	0.178 (0.056–0.564)	0.003	0.171
Shrinkage of nodal lesion†	0.087 (0.007–1.070)	0.056	0.081 (0.020–0.324)	0.000	0.923
Residual of primary lesion (No vs Yes)	0.181 (0.048–0.684)	0.012	0.298 (0.159–0.561)	0.000	0.531
Residual of nodal lesion (No vs Yes)	0.132 (0.040–0.438)	0.001	0.214 (0.115–0.400)	0.000	0.503

†as continuous covariates entered into equations

absence of residual tumor cells in primary nasopharyngeal lesions, and neck lymph node metastatic lesions were significantly associated with OS in the whole population. However, in the multivariate Cox regression analysis, which used each of these four factors were, T stage binary variable (T3–T4 and T1–T2) and the interaction of these two variables were included as covariates. However, the interactions were not significant. Moreover, these four factors were consistently associated with OS in both the N0-N1 and N2-N3 subgroups. However, the interactions were not significant (Table 3). These results showed that at least N stage may not be influenced by the prognostic value of TVRRs.

Discussion

At present, clinical staging is the most important tool for predicting the prognosis of NPC. However, clinical staging is based only on the parts and regions invaded by tumors and does not consider tumoral heterogeneity. Moreover, it is essential in building a diverse prediction model.

Induction chemotherapy plays an important role in the treatment of locally advanced NPCs. A prospective, multicentered, randomized controlled clinical study has shown that induction chemotherapy did not only reduce the metastatic rate of locally advanced NPCs but also improve the OS rate of patients [5]. According to the literature, other than reducing tumor burden, induction chemotherapy has the following benefits: It helps protect organs around the tumor that are at risk during radiotherapy treatment, improves radiation dose, reduces the incidence rates of radiotherapy infections, increases local control rates, improves blood supply and radiosensitivity, and reduces the risk of subclinical metastasis. An increasing number of scholars believe that radiotherapy must be tailored for each individual patient with NPC, and radiation doses should be adjusted based on specific patient-related factors. Grade III–IV toxic reactions due to the use of high doses of radiotherapy for short or long periods of time have been a topic of interest. A method that can predict the short- and long-term efficacy of radiotherapy is used for the development of tailored treatment plans for NPC.

Several factors influence the efficacy of radiotherapy. Of these, multiple drug resistance and radiotherapy resistance are particularly important. Chorna *et al* [6] have irradiated cells sensitive to radiation and resistant to doxorubicin using an X-ray machine and have detected the expression of Bax, Bad, and Bcl-2 proteins before and after radiation. Moreover, they have found a significant difference in the expression of the proapoptotic proteins Bax and Bad and antiapoptotic protein Bcl-2 in cells sensitive to radiation, with the expression of Bax and Bad increasing and that of Bcl-2 decreasing. In contrast, the expression of these proteins in irradiated cells resistant to doxorubicin did not change significantly. The same study has reported increased DNA repair capacity and decreased DNA damage in X-ray irradiated cells resistant to doxorubicin and has concluded that this may explain the resistance of these cells to X-ray radiation treatment. Leng *et al*.[7] have applied radiation treatment to a tongue squamous cell carcinoma cell line (Tca 8113) and Tca 8113/CBDEA cell line resistant to drugs and used an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay to detect survival curves for both cell lines. Their results showed that the ID50 of the Tca 8113/CBDEA cell line was 1.24 times than that of the Tca 8113 cell line. They have concluded that the tongue squamous cell carcinoma cell line resistant to drugs was also resistant to radiotherapy. Several other studies have showed that drug resistance by mutations in circulating tumoral DNA may be correlated to radiotherapy resistance. [8-10] The findings of the aforementioned studies have suggested that some head and neck tumor cells resistant to drugs are not sensitive to radiation, whereas cells sensitive to chemotherapy are also sensitive to radiotherapy. However, the conclusions obtained in these studies are

based on fundamental research. Similar findings have not been reported in the clinical observations of NPCs.

The results of the present clinical study of locally advanced NPCs are in accordance with those in the literature. We found that higher TVRRs before induction chemotherapy were associated with lower residual tumor rates. Furthermore, NPCs insensitive to chemotherapy were also insensitive to radiotherapy, and the presence of residual tumor cells after radiotherapy was positively correlated to the OS rate.

In conclusion, this retrospective study showed that the tumor regression status of NPCs after induction chemotherapy may be positively correlated to residual tumor cells after radiotherapy and that residual tumor cells influenced survival rates. The findings indicated that the TVRR after the induction chemotherapy of NPCs may be an effective predictive indicator of postradiotherapy efficacy. A prospective study must be conducted to validate the findings of the present study. Patient-specific treatment plans for NPC must be used to reduce the adverse reactions of radiotherapy.

Conflicts of interest

The authors declare no potential conflicts of interest.

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