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Original Article

The impact of target dosimetry on patients' locoregional recurrence in nasopharyngeal carcinoma: A propensity score-matched analysis

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ABSTRACT

Purpose: To analyze the impact of target dosimetry using propensity score matching (PSM) on patients' locoregional recurrence for nasopharyngeal carcinoma (NPC) and to find significant dose–volume factors of recurrence.

Methods: Sixty-eight nasopharyngeal carcinoma (NPC) patients with recorded locoregional recurrence were enrolled in this study. These patients were treated with IMRT in 2009–2010 in our department. Another 198 NPC patients without recurrence were randomly selected from the same treatment time period. The median follow-up time for all patients was 49.0 months. PSM was performed to match the recurrence and nonrecurrence cohorts. Dose–volume histograms (DVHs) of treatment planning were extracted for statistical analysis. Cox hazard model and Kaplan-Meier log-rank analysis were performed to evaluate correlations between PTV dose coverage and local/region recurrence.

Results: Propensity score matching balanced the clinical factors in two matches. Univariate cox survival model showed D90 and D95 were significantly correlated to the recurrence, and the D90 was the most significant ($p = 0.036$) one. The results of multivariate analysis show that only D90 is required for recurrence prediction when collinear dosimetric factors are considered. KM log-rank analysis showed that patients have significant local/regional control differences (p-value = 0.036, log-rank) in the D90 >101% and D90 <101% groups.

Conclusion: D90 corresponds to significant dose–volume factors. PTV dose coverage has a significant impact on locoregional recurrence in NPC clinical routine patients.

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy that is common in Southeast Asia, the Mediterranean basin, and South China [1]. Radiotherapy is the main treatment modality of NPC. In recent years, with the widespread use of intensity modulated radiotherapy (IMRT), which optimizes radiation deposition in the tumor while sparing adjacent normal structures, the 5-year local control and overall survival rates of NPC have reached above 90% and 80%, respectively [2]. However, Ou et al. [3] reported that the major failure patterns in NPC patients are metastasis (51.4%) and locoregional recurrence (40.1%).

The correlation between tumor control and dose coverage was evident. Some biological models, such as the TCP model [4], are used to calculate the theoretical probability of tumor control. However, it is difficult to establish a precise model of TCP and target dosimetry under the influence of other relevant factors, such as prescription dose, tumor delineation and target margin. Following strict restrictions on the enrollment criteria, the data of clinical trials show that non-adherence to protocol-specified RT requirements are associated with reduced survival and local tumor control and can potentially lead to increased toxicity [5–7]. It is not clear whether this relationship still exists for routine clinical patients.

Clinical factors, such as T/N stage, impact patients' local/region control [2]. Meanwhile, it is more difficult to create a clinical acceptable treatment plan for patients with advanced NPC than ones without. Dosimetrists may need more planning time to balance the target coverage and normal tissue sparing. Therefore, the quality of these treatment plans may degrade. This indicates that target coverage, clinical stage and patients' local/region control are related to each other. Using traditional statistical methods, we may need a large number of samples to determine the true relationship between plan quality and patients' local/region control. In addition, each patient may have many interrelated dosimetric indices to describe plan quality. If we put all these dosimetric indices and clinical factors together, it may further confuse the results.

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In this study, propensity score matching (PSM) was used to reduce the influence of the clinical factors on patients' local/region control. PSM is an analytical tool that has been demonstrated to reduce bias in observational studies by balancing known confounding variables in compared treatment groups [8]. After that, we try to find dosimetric indices related to local/region control for routine clinical patients by univariate and multivariate analysis.

Materials and methods

Study population

This study enrolled 266 NPC patients who received curative treatment with IMRT in our department during 2009–2010. Briefly, 68 patients recorded with local/regional recurrence were included, and the other 198 patients were randomly selected from a no-recurrence group (local recurrence corresponding to primary lesion while regional recurrence corresponding to lymph node target volume); the median follow-up time was 49.0 months. All patients received complete radiotherapy, together with detailed clinical diagnosis and successive follow-up.

Data quality assurance processing was carried out to verify the correctness and integrity of treatment planning data. First, we checked the electronic medical record (EMR), verifying the detailed RT records, including fractions, RT duration, prescriptions, and linac machine, to make sure each patient received a complete treatment. Patients with no clear record of chemotherapy were excluded. Next, according to patients' ID, we reviewed radiotherapy plans in the Pinnacle treatment planning system (8.0 m. Philips Healthcare, MA). Patient ID, RT structure, PTV label and DVH (dose volume histogram) integrity were examined. Clinical characteristics were retrospectively reviewed from a clinical database under the approval of the Institutional Review Board. All patients were staged according to the 8th American Joint Committee on Cancer/Union for International Cancer Control staging system.

Treatment planning

In this study, NPC patients received two types of radiotherapy prescriptions, 70.4 Gy or 66 Gy, based on their clinical stage. For local advance patients, four different planning target volumes (PTV70, PTV66, PTV60, and PTV54) were contoured. For regionally advanced patients, three different target volumes (PTV66, PTV60 and PTV54) were contoured. The margin between CTV and PTV was 3–5 mm; physicians may modify PTV base on personal experience. The treatment fraction was 32 and 30 for locally advanced and regionally advanced patients, respectively.

Local and regional recurrences correspond to primary lesion and lymph node target volume, respectively. For locally advanced patients, PTV70 was used to cover the primary lesion (related with local recurrence outcome), while PTV66 was used to cover the lymph node (related with regional recurrence outcome). For regionally advanced patients, PTV66 covers both target volume area.

All patients were treated by 6 MV photon with IMRT in the Pinnacle treatment planning system. All deliverers were based on laser setup.

Follow-up

Patients were followed up every three months in the first two years after radiotherapy, then every six months from year two through year five, and then annually. In each follow-up visit, physical examinations, including direct or indirect nasopharyngoscopy, were performed. MRI of head and neck were required every three to six months in the first three years.

The local and regional recurrence were generally combined (named as locoregional recurrence) for analysis in the NPC study, which aimed to find the overall relationship between PTV dose coverage and locoregional recurrence, rather than some detailed classification result.

Propensity score matching

To balance clinical variables between recurrent and non-recurrent patients, we used multivariable logistic regression to generate propensity scores for all match-eligible patients [8]. Patients' age, sex, T stage, N stage, induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy were inputted into model for matching. The sex, T stage, N stage, induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy were considered category variables. Age was considered a continue variable. We used a one-to-one match strategy with nearest-neighbor matching methodology. The MATCHIT [9,10] package with R (version 3.5) was used to perform PSM.

Statistical analysis

In this study, we only focused on the target doses. The dose–volume indices from D0 to D90 in steps of 5 were calculated. Dx represent the percentage of prescription dose that covers x% of the PTV.

In univariate analysis, log-rank tests were performed for category variables, such as sex, T stage, N stage, induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy. Cox proportional hazards regression analyses were performed for continuous variables, such as age and dose–volume indices. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

In multivariate analysis, we used the LASOO (least absolute shrinkage and selection operator) regression model to select the most important factor from multivariate analysis. Because dose–volume indices are highly correlated, it was difficult to find important features by traditional statistical methods. By using LASSO, we can find the strongest predictive power feature from a set of highly correlated features. A 5-fold cross-validation was performed to find an appropriate hyperparameter.

Results

In our 266 patients' dataset, the numbers of patients prescribed with 70.4 Gy and 66 Gy were 160 (60.2%) and 106 (39.8%), respectively. In the recurrence group, 32 (47.1%) and 36 (52.9%) patients were prescribed 70.4 Gy and 66 Gy, respectively. Details of demographic profiles and PSM are shown in Table 1. There was no difference between nonrecurrent and recurrent groups for clinical factors after PSM. The *p*-values of the T stage, N stage, induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy were 0.328, 0.312, 0.356, 0.959 and 0.901 respectively.

Fig. 1 shows the *p*-value of cox hazard model for the dose–volume indices and clinical factors. The p values of D90 and D95 were less than 0.05. The most significant feature was D90 ($p = 0.035$).

Fig. 2 shows that the dose-value indices were highly correlated. D100, which represents minimum dose, was the most independent dosimetric factor, which was only highly correlated with D95 and D90 ($R > 0.05$). Fig. 3 shows the results of hyperparameter λ adjusted by 5-fold cross-validation. With minimum partial likelihood deviance, only D90 was left.

The median value of D90 was 101%. We divided patients into D90 over median value (D95 >101%) and D95 less than median value (D95 <100%) groups. The distribution of the D90 was pre-

Table 1
Baseline characteristics for all patients and patients matched on propensity scores.

Characteristics	Entire cohort (n = 266)			Propensity score-matched cohort (n = 140)		
	Nonrecurrent (n = 198)	Recurrent (n = 68)	S.D. (P)	(n = 68)	Recurrent (n = 68)	S.D. (P)
Age[#]						
Mean ± SD	50.0 ± 12.3	50.0 ± 10.7	−0.7164 (0.973)	51.5 ± 12.5	50.0 ± 10.7	0.3529 (0.543)
Sex[*]						
Male	154 (0.78)	53 (0.78)	−0.0016 (0.668)	46 (0.68)	53 (0.78)	−0.1029 (0.689)
Female	44 (0.22)	15 (0.22)		22 (0.32)	15 (0.22)	
T stage[*]						
T1	59 (0.30)	12 (0.18)	−0.1215 (0.088)	12 (0.18)	12 (0.18)	0.0000 (0.328)
T2	56 (0.28)	23 (0.34)	0.0554	22 (0.32)	23 (0.34)	0.0147
T3	56 (0.28)	21 (0.31)	0.0260	20 (0.29)	21 (0.31)	0.0147
T4	27 (0.14)	12 (0.18)	0.0401	14 (0.21)	12 (0.18)	−0.0294
N stage[*]						
N0	25 (0.13)	4 (0.06)		2 (0.03)	4 (0.06)	
N1	93 (0.47)	25 (0.37)	−0.1020 (0.035)	30 (0.44)	25 (0.37)	−0.0735 (0.312)
N2	56 (0.28)	28 (0.41)	0.1289	24 (0.35)	28 (0.41)	0.0588
N3	24 (0.12)	11 (0.16)	0.0406	12 (0.18)	11 (0.16)	−0.0147
Induction chemotherapy[*]						
Yes	173 (0.87)	60 (0.88)	0.0086 (0.646)	62 (0.91)	60 (0.88)	−0.0294 (0.356)
No	25 (0.13)	8 (0.12)		6 (0.09)	8 (0.12)	
Concurrent chemotherapy[*]						
Yes	138 (0.70)	47 (0.69)	−0.0058 (0.953)	47 (0.69)	47 (0.69)	0.0000 (0.959)
No	60 (0.30)	21 (0.31)		21 (0.31)	21 (0.31)	
Adjuvant chemotherapy[*]						
Yes	118 (0.60)	26 (0.38)	−0.0217 (0.646)	24 (0.35)	26 (0.38)	0.0294 (0.901)
No	80 (0.40)	40 (0.59)		44 (0.65)	40 (0.59)	

S.D: represent standardized difference.
[*] Log-rank test.
[#] Cox proportional hazards regression analyses.

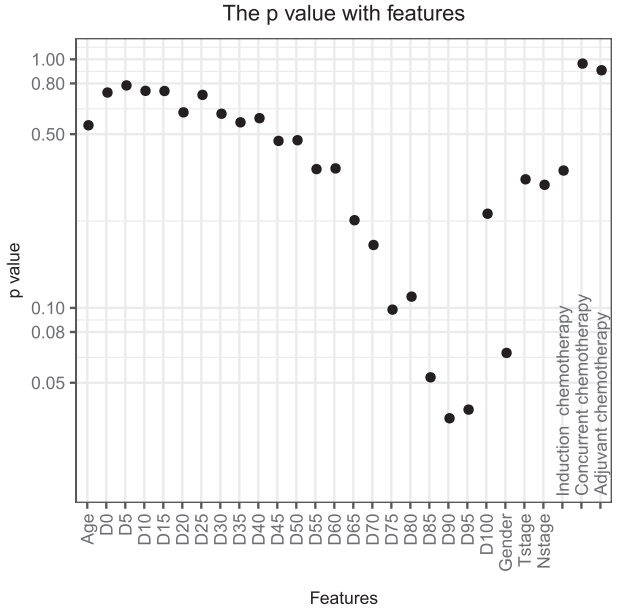

Fig. 1. The p-values of the univariate analysis.

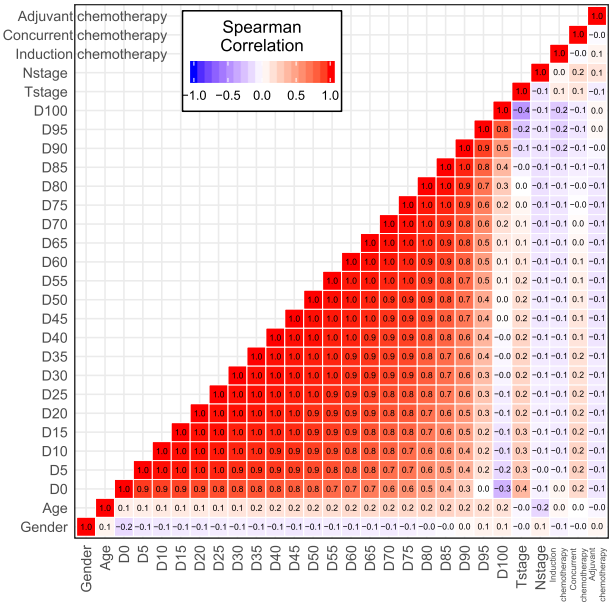

Fig. 2. The correlation heatmap between features.

sented in Fig. 4A. Fig. 4B shows the Kaplan–Meier plot of D95. The log-rank test shows that these two groups were significantly different (p = 0.036).

Discussion

The purpose of this study was to analyze the impact of target dosimetry on patients' locoregional recurrence. There are two novelties in this study. First, the effect of clinical factors on patient's outcome was filtered out using propensity score matching. Second, the patient data is based on the routine patient population instead of on clinical trial data, which means the result from our study may be more applicable for general patients. The univariate cox analysis result reveals that many dose–volume factors have an effect on recurrence. Among them, D90 has the minimum p-value. This result was also demonstrated in the LASSO analysis.

T/N stage is correlative with patients' outcome [2,11,12]. This is because a patient's prescription and treatment target are related to

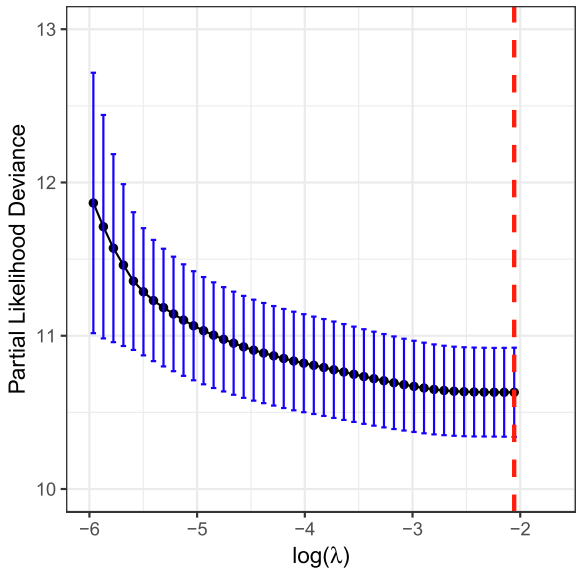

Fig. 3. Feature selection using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model. The hyperparameter λ was adjusted by 5-fold cross-validation. The partial likelihood deviance was plotted versus log(λ). Dotted vertical lines were drawn at the minimum value of partial likelihood deviance.

the T/N stage. It is more difficult to create a high-quality treatment plan for advanced cancer patients because the target volume is larger and prescription is higher. Our results showed the T stage was weakly correlate to D0 and D100. The spearman correlation coefficients were 0.4 and −0.4, respectively (Fig. 2). D0 and D100 represent the minimum and maximum doses of PTV. As T stage increases, the minimum dose of PTV decreases, and the maximum dose of PTV increases. This means that dosimetrists and physicians may sacrifice the dose coverage and uniformity of the target to reduce the doses to OARs.

To fully investigate the impact of dosimetric factors on patient locoregional recurrence, the correlation between locoregional recurrence and T/N stage needs to eliminate. We have removed this correlation using PSM. Without PSM, T stage, N stage and may dosimetric factors were correlated with patients' locoregional recurrence. It will be difficult to explain this result; all these factors are not independent.

Although D90 was the most significant dosimetric factor in our analysis. The difference between D90 and D95 was small ($p = 0.036$ and $p = 0.038$). This means that using D95 prescriptions is still appropriate. D95 is a commonly used dose–volume constraint, and many clinical trials use this value to determine prescription dose [13]. There is not much evidence to demonstrate that this parameter is optimal. ICRU 83 reports do not recommend any particular value of dose volume indices for a prescription [14]. They believe D50 may be a good measure of a typical absorbed dose in a relatively homogeneously irradiated tumor. However, our study shows that there is no correlation between D50 and locoregional recurrence ($p = 0.47$). This finding means recurrence may be mainly correlated to the low-dose region of the PTV.

Meanwhile, near-minimum absorbed dose D99 and D98 were usually required in routine clinical practice and in clinical trials. Our study also shows that D99 and D98 were not correlated with loco-region recurrence ($p = 0.08$ and $p = 0.17$, cox hazard regression). The log-rank analysis also showed there is not difference between two groups divided by D99 and D98 (Fig. 5). This means D99 and D98 were less significant than D90 or D95. This finding indicates that only a sufficiently large region lack of radiation may have impact on patients' prognosis.

In this study, we used routine clinical data for analysis. There are many differences between routine clinical practice and clinical trial patients. Most clinical trials strictly regulate the eligibility and ineligibility criteria for patient enrollment. For clinical practice, we cannot select patients based on their conditions. Clinical trials also strictly regulate the treatment for patients, such as chemotherapy and biologic therapy. For radiotherapy, most multi-institution trials have a centralized quality assurance process. For clinical routine data, this process was only based on physicians' personal experience. Our results demonstrate that D90 is the key clinical dose–volume index for NPC radiotherapy, even in the presence of large amounts of perturbations.

This study has some limitations. We only considered the highest prescription target. Other targets may have some effects on patients' prognoses. We only focused on target coverage and did not include OAR sparing. To get a highly credible results, more data or a multi-institution study is required.

To conclude, the dose coverage of PTV, especially the minimum absorbed dose that covers 90% of the volume of the highest prescription PTV, has an impact on recurrence in NPC patients.

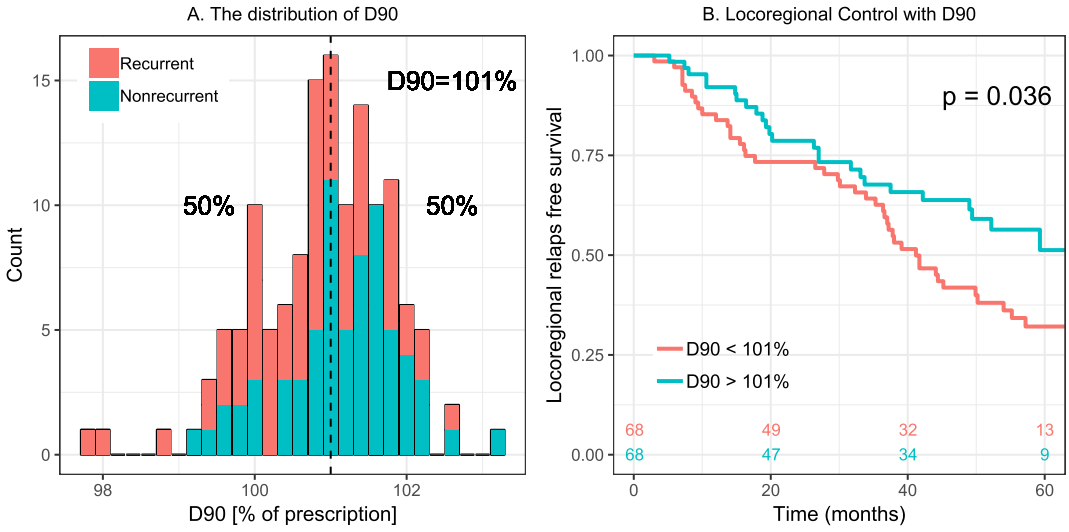

Fig. 4. Kaplan–Meier Log-rank Survival analysis of D90. (A) The distribution of D90. (B) The Kaplan-Meier log-rank survival analysis of D90.

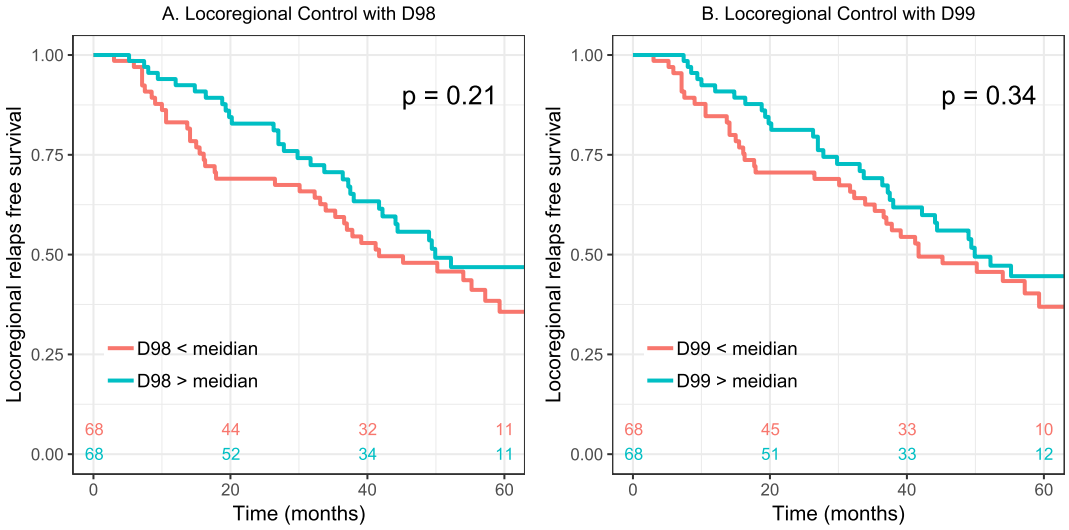

Fig. 5. Kaplan–Meier Log-rank Survival analysis of D98 and D99. (A) The Kaplan–Meier log-rank survival analysis of D98. (B) The Kaplan–Meier log-rank survival analysis of D99.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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