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HEAD AND NECK

Radiomics on multi-modalities MR sequences can subtype patients with non-metastatic nasopharyngeal carcinoma (NPC) into distinct survival subgroups

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Abstract

Objectives To explore and evaluate the feasibility of radiomics in stratifying nasopharyngeal carcinoma (NPC) into distinct survival subgroups through multi-modalities MRI.

Methods A total of 658 patients (training cohort: 424; validation cohort: 234) with non-metastatic NPC were enrolled in the retrospective analysis. Each slice was considered as a sample and 4863 radiomics features on the tumor region were extracted from T1-weighted, T2-weighted, and contrast-enhanced T1-weighted MRI. Consensus clustering and manual aggregation were performed on the training cohort to generate a baseline model and classification reference used to train a support vector machine classifier. The risk of each patient was defined as the maximum risk among the slices. Each patient in the validation cohort was assigned to the risk model using the trained classifier. Harrell's concordance index (C-index) was used to measure the prognosis performance, and differences between subgroups were compared using the log-rank test.

Results The training cohort was clustered into four groups with distinct survival patterns. Each patient was assigned to one of the four groups according to the estimated risk. Our method gave a performance (C-index = 0.827, $p < .004$ and C-index = 0.814, $p < .002$) better than the T-stage (C-index = 0.815, $p = .002$ and C-index = 0.803, $p = .024$), competitive to and more stable than the TNM staging system (C-index = 0.842, $p = .003$ and C-index = 0.765, $p = .050$) in the training cohort and the validation cohort.

Conclusions Through investigating a large one-institutional cohort, the quantitative multi-modalities MRI image phenotypes reveal distinct survival subtypes.

Key Points

- *Radiomics phenotype of MRI revealed the subtype of nasopharyngeal carcinoma (NPC) patients with distinct survival patterns.*
- *The slice-wise analysis method on MRI helps to stratify patients and provides superior prognostic performance over the TNM staging method.*
- *Risk estimation using the highest risk among slices performed better than using the majority risk in prognosis.*

En-Hong Zhuo and Wei-Jing Zhang contributed equally to this work.

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Keywords Nasopharynx · Magnetic resonance imaging · Radiomics · Survival analysis

Abbreviations and acronyms

AJCC	American Joint Committee on Cancer
CI	Confidence interval
EBV	Epstein-Barr virus
GC	Gastric cancer
IMRT	Intensity-modulated radiation therapy
LRFS	Locoregional recurrence-free survival
NPC	Nasopharyngeal carcinoma
PGL	Primary gastric lymphoma
ROI	Region of interest
TNM	Tumor, node and metastasis
UICC	Union for International Cancer Control

Introduction

Nasopharyngeal carcinoma (NPC) is a prevalent head and neck cancer, with the highest incidence occurring in South China [1]. Intensity-modulated radiation therapy (IMRT) is currently the standard treatment for NPC, provided that resources are available. Although advances in therapeutic techniques have contributed to improved clinical outcomes for patients with NPC, the mortality rate remains high [2]. As far as we are aware, the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system is the most widely used prognostic tool for predicting survival outcomes for patients with NPC [3]. Intriguingly, the outcomes of patients with the same stage of NPC often vary [4]. Recently, several prognostic factors for identifying NPC patients with a poor clinical outcome have been identified. It has been reported that the C-reactive protein/albumin ratio, morphologic nodal volume, and urine Epstein-Barr virus (EBV) DNA analysis may potentially be applicable as independent prognostic factors for NPC [5–7]. Moreover, several investigations suggested that HOXC6, P53R2, and long non-coding RNA PVT1 have a diagnostic value in the prognosis of NPC [8–10]; however, their use is limited in clinical practice. Therefore, there is an urgent need to develop more effective yet non-invasive prognostic tools that could help clinicians stratify NPC patients for tailored treatment.

Radiomics, a promising field studying the relationship between medical imaging and diseases, is gradually becoming used as an auxiliary means of analyzing and diagnosing various diseases, having shown potential in clinical prognoses [11–15]. Recent studies showed that radiomics features of MRI could serve as prognostic factors in NPC [16–20]. Using such radiomics features, Bin et al developed models to provide improved prognostic ability [16] and predict local and distant failure in advanced NPC [17]. The radiomics features of MRI were also used to predict treatment response to chemoradiotherapy [18] and induction chemotherapy [19] in patients with NPC. However, the abovementioned reports focused more on advanced NPC, without considering cases with early- or middle-stage disease. Furthermore, the patients enrolled in these studies were not irradiated with IMRT, and the studies do not therefore reflect the recent diagnostic and therapeutic advances. Mao et al proposed several prognostic predictors for NPC, but the patients in this study received different therapies, which might affect the survival of patients [20].

The purpose of this study was to investigate the prognostic power of radiomics extracted from multiple modalities MRI on NPC patients with primary tumor. The primary task is to determine whether the MRI-based radiomics can stratify NPC into distinct survival patterns in the early or middle stage NPC.

Materials and methods

Patients

This retrospective study was approved by the institutional review board and the requirement for written informed consent was waived (Approval No. GZR2018-050). A total of 658 consecutive patients who presented with non-metastatic NPC at Sun Yat-sen University Cancer Center between January 2010 and January 2013 were enrolled in this study. The eligibility criteria were as follows: (a) pathological diagnosis of NPC; (b) without evidence of distant metastasis; (c) underwent radical IMRT according to the standard guidelines; (d) without a primary tumor in other parts of the body; (e) complete clinical and detailed MRI report data were available. The patients were randomly divided into a training cohort ($n = 424$) and a validation cohort ($n = 234$), making sure that the ratio between the number of patients in the training group and that in the validation group was around 2:1 while the events in both groups were roughly equal.

Demographic and clinical characteristics were collected including gender, age, T-stage, N-stage, and overall stage. Tumor staging was performed in consensus according to the American Joint Committee on Cancer TNM Staging System Manual, 8th Edition. Patient follow-up was measured from the first day of therapy to the day of the last examination or death. Patients were examined at least every 3 months during the first 2 years, with follow-up examinations every 6 months for the 3 years thereafter or until death.

MRI acquisition and image pre-processing

MRI was performed on a 3.0-T scanner (Discovery MR750; GE Healthcare). T1-weighted (T1-w), T2-weighted (T2-w), and contrast-enhanced T1-weighted (CET1-w) MR images were assessed for each patient. MRI parameters for each sequence are described in Supp. 1. All images were co-registered to the T1-w image for each subject through standard procedures in FLIRT (FMRIB's Linear Image Registration Tool, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT). Regions of interest (ROI) were first drawn by four experienced radiologists manually using the software Analyze Pro (https://analyzedirect.com/analyzepro/). They were required to draw cautiously all discernable tumor regions along axial directions, in which imaging has a high resolution of 0.43 mm × 0.43 mm. After that, we applied the classical active contour model to obtain the segmented ROI for some small or tiny tumors in MATLAB. The labeled boundary drawn by the radiologists was used to initialize the active contour. Any disagreements were resolved through negotiating until full consent was derived by the four radiologists. The raw image type we used was DICOM. Supp. 2 provides a figure showing the process of segmentation.

Radiomics feature calculation

For each modality, a total of 1621 radiomics features were extracted for each ROI on each slice. The radiomics include the first-order statistical features, shape features, statistics-based texture features, wavelet features, and Gabor features (Supp. 1). All of the feature extraction methods were implemented by us based on built-in functions in MATLAB and formulas in the supplementary files of [11]. Features extracted from T1-w, T2-w, and CET1-w images were concatenated according to the slices, thereby resulting in 4863 features per slice. The raw data in this paper has been successfully uploaded and locked onto Research Data Deposit with an RDD number of RDDA2019000986.

Baseline building to stratify NPC into distinct survival subtypes and prognosis model

In the training cohort, we firstly employed an entropy-based consensus clustering method [21] on each sample MRI slices to obtain a consensus partition with C clusters. The cluster number C was set to a large number to ensure that the samples with a high risk would not be mixed up with those with a low risk. An aggregation step was then performed to merge clusters with similar survival patterns. Clusters with neighboring survival curves were aggregated to new subgroups, and a final total of M stratified subgroups was obtained. The subgroup number M was set manually. Risk scores from 1 to M were then used to quantify the survival status of each subgroup, with a lower risk score indicating a greater survival rate. The subgroups obtained in the training cohort then served as a baseline to evaluate the risk for a new query patient. Finally, a prognostic model was built by using the benchmark model of a multi-class support vector machine with a Gaussian kernel. Detailed information of the SVM training process was supplied in Supp. 1. The obtained baseline subgroups were numbered, which serves as the subject label in training the prognostic classifier.

In the validation cohort, each patient is assigned to one of the obtained baseline subgroups. Since the ROIs for each patient were drawn in multiple consecutive slices, we first computed the radiomics feature for each slice of each subject. Each slice was treated as a sample and was fed into the prognostic model to have a predicted label. In assigning the subject to the right subgroup, two decision strategies named "voting strategy" and "highest strategy" were proposed. The voting strategy performed a majority vote on the subgroup labels of the MRI slices for each subject. The highest strategy assigned a patient to the subgroup with the highest risk score among all the subject's slices. The risk scores of the patients were set as the subgroup they were assigned to. For example, ROI slices of a patient were assigned the risk scores of 2, 3, 3, 4, 3, as shown in Fig. 1. The voting strategy decided the majority score as the risk of the patient, which was 3. The highest strategy decided the highest score as the risk of the patient, which is 4. The entire workflow of the analysis is briefly and precisely summarized in Fig. 1.

Comparison methods

The T-stage in the TNM staging system was used for a comparison stratification method that involved features of the primary tumor only. In addition, TNM overall stage was also used for further comparison to show the stratification potential of our method. For the purpose of comparison, risk scores of patients were set from 1 to 4, corresponding to T1 to T4 in T stages and stage I to stage IV-a in the TNM overall stage.

Statistical analysis

The prognosis ability of the stratification results and the staging system was measured using the Harrell's concordance index (C-index) with 95% confidence interval (CI). Student's t test was performed to compare the C-index of different methods. The survival curves were plotted with the Kaplan-Meier method, and differences were compared with the log-rank test. A two-tailed p value of less than .05 was considered to indicate a significant difference. Statistical analyses were performed with R 3.4.1 (http://www.R-project.org) and MATLAB platform (www.MathWorks.com).

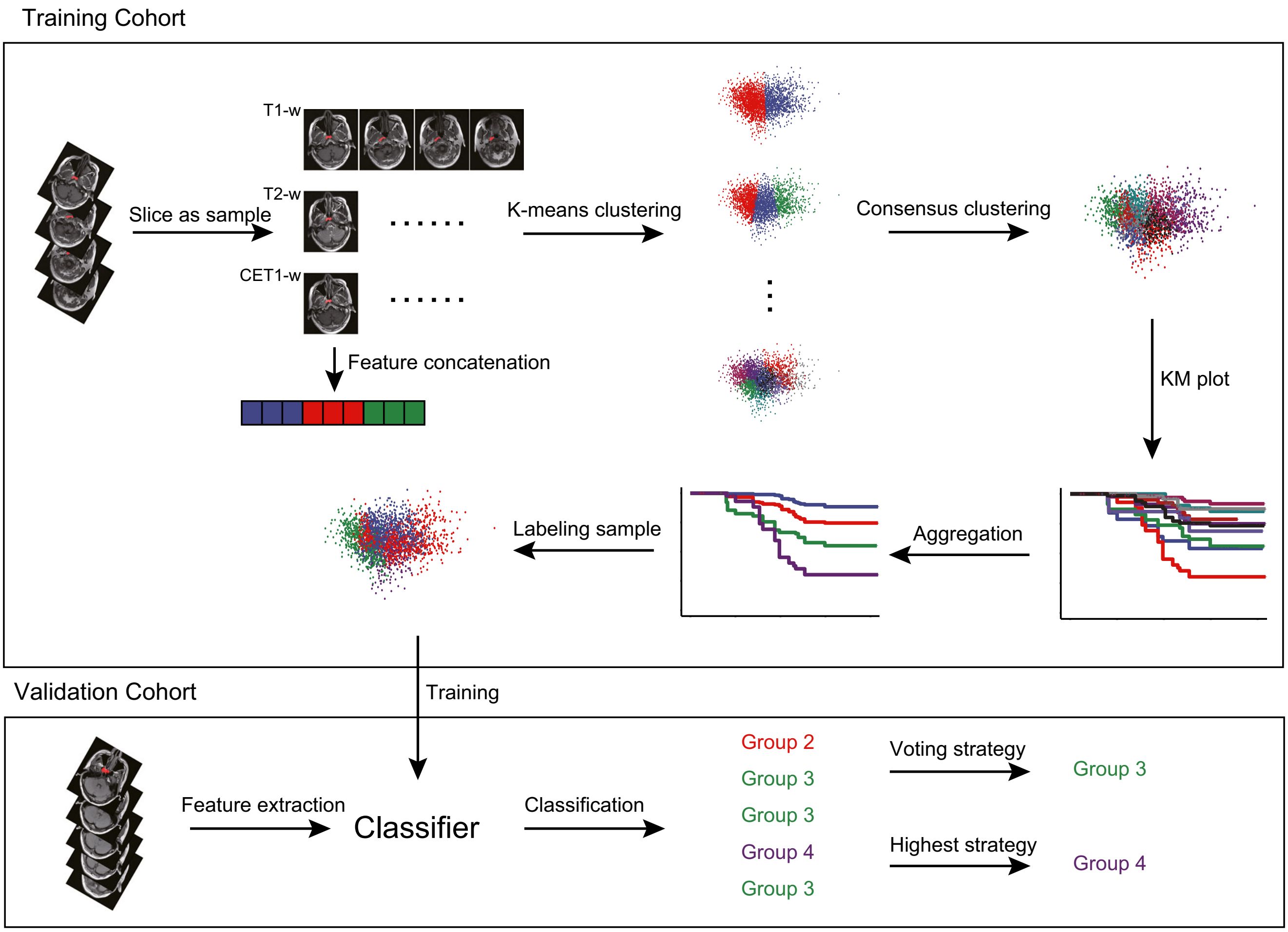


Fig. 1 Flowchart showing the process of stratification. Radiomics features were extracted for each MRI slice. In the training cohort, consensus clustering and aggregation were performed on the sample slices and four subgroups were obtained. A classifier was trained based on the stratification results. For a query patient, each MRI slice was categorized into one of the subgroups. Decision strategies were finally performed to decide the risk of the patient

Results

Characteristics of the patients

In total, 658 NPC patients were included, and the demographic and clinical characteristics of the patients in the training and validation cohorts are summarized in Table 1. Within the median follow-up duration of 63.0 months (range, 4.6–83.4 months), 29 of 658 (4.0%) patients died (17 of 424 [4.0%] patients died in the training cohort and 12 of 234 [5.1%] patients died in the validation cohort). There were 66 cases of grade I, 158 of grade II, 258 of grade III, and 176 of grade IV-a tumor according to the 8th edition of the UICC/AJCC staging system for nasopharyngeal carcinoma.

Subtyping by radiomics on the training cohort is significantly correlated with survival

K-means clustering with *K* ranging from 2 to 50 was performed on the training cohort. Each value of *K* was performed 10 times, with randomly selected initial centers each time, resulting in 490 basic partitions being obtained for consensus clustering. The cluster number C of the entropy-based consensus clustering method was set from 2 to 10. Kaplan-Meier curves were then plotted for the nine consensus partitions, and the partition with the lowest curves (C = 10) was chosen for the following aggregation. According to the Kaplan-Meier curves for C = 10, the number of the final groups *M* was manually set to 4, and the clusters were aggregated with similar survival (Fig. 2). Risk scores were set from 1 to 4 for the aggregated groups. Visualization of radiomics features with different groups in the training cohort are shown in Fig. 3a using t-SNE.

Two different strategies were applied to the patients in the training cohort respectively. The stratification baseline resulting from the voting strategy yielded a C-index of 0.804 (95%CI: 0.712–0.896), and the baseline resulting from the highest strategy yielded a C-index of 0.827 (95%CI: 0.699–0.955). In contrast, T-stage yielded a C-index of 0.815 (95%CI 0.655–0.964) and TNM overall stage yielded the highest C-

Table 1 Demographic and clinical characteristics of patients in training and validation cohorts

Variable	Training cohort ($N = 424$) No. (%) of Patients	Validation cohort ($N = 234$)
Age (years)		
Mean (SD)	45.3 (11.7)	44.4 (10.3)
Median (IQR)	45 (38–53)	44 (37.3–50)
Sex		
Male	315 (74.3)	167 (71.4)
Female	109 (25.7)	67 (28.6)
T category		
T1	93 (21.9)	79 (33.8)
T2	59 (13.9)	25 (10.7)
T3	162 (38.2)	74 (31.6)
T4	110 (25.9)	56 (23.9)
N category		
N1	104 (24.5)	54 (23.1)
N2	256 (60.4)	150 (64.1)
N3	59 (13.9)	23 (9.8)
N4	5 (1.2)	7 (3.0)
Overall stage		
I	37 (8.7)	29 (12.4)
II	91 (21.5)	67 (28.6)
III	182 (42.9)	76 (32.5)
IV-a	114 (26.9)	62 (26.5)
Follow-up time		
Median (IQR)	63.0 (56.1–67.1)	62.9 (57.1–66.3)

SD, standard deviation; *IQR*, interquartile range

index, which is 0.842 (95%CI 0.717–0.968). The survival curves and the log-rank test results of four stratification methods in the training cohort are shown in Fig. 4.

Radiomics on the validation cohort yields a high survival prognostic performance

For each patient in the validation cohort, the MRI slices with an ROI were classified by the SVM classifier into one of the four subgroups. Visualization of radiomics features with different groups in the validation cohort are shown in Fig. 3b. Two different strategies were then applied to the patients in the validation cohort respectively. The stratification results obtained from the voting strategy yielded a C-index of 0.648 (95%CI 0.391–0.905), and the results obtained from the highest strategy yielded the highest C-index, which is 0.814 (95% CI 0.668–0.961). In contrast, T-stage yielded a C-index of 0.803 (95%CI 0.651–0.955) and TNM overall stage yielded a C-index of 0.765 (95%CI 0.579–0.952). The survival curves and the log-rank test results of four stratification methods in the validation cohort are shown in Fig. 5.

From the results, we found that the highest strategy performed better than the voting strategy and the T-stage in both the training cohort and validation cohort. In further comparison with the TNM overall stage, the highest strategy yielded C-indices a little smaller than the overall stage in the training cohort but relatively larger than the overall stage in the validation cohort. Moreover, the difference of C-indices between two cohorts resulting from the highest strategy was 0.013, while the difference resulting from the TNM staging system was 0.077. This indicated that the highest strategy led to smaller performance fluctuation between different cohorts and thus was more stable than the TNM staging system.

Table 2 shows the p value of Student's t test comparing the C-index between different methods. There is no significant difference ($p < .05$) between any pair of methods. However, we could consider the p value as the coincidence score of the prognostic ability between the methods. A higher p value indicated the stronger coincidence of prognostic ability. Lower p values should be considered together with the C-index value. A lower p value with a large C-index indicated better performance, while a lower p value with a small C-index indicated poorer performance. Thus, we could find from Table 2 that the highest strategy showed its prognostic ability coincident with the standard TNM staging system in both the training cohort and the validation cohort. The voting strategy showed a high coincidence in the training cohort but low coincidence in the validation cohort. These results showed that radiomics features were feasible to stratify NPC patients with the comparative prognostic ability with the standard TNM staging system, and the highest strategy was more robust than the voting strategy.

To further investigate the interaction of our method and TNM stage, we evaluated the performance collaborating the highest strategy and TNM stage. Detailed methods and results are given in Supp. 1.

Discussion

In our study, we successfully stratified patients with non-metastatic NPC by using MRI-based radiomics features. Experimental results demonstrated that the stratification based on radiomics features outperformed the T-stage on prognostic ability. Since we aimed to explore the prognostic ability of radiomics features of primary tumors, this study did not exploit information on lymph nodes. However, the results of our method demonstrated a performance competitive to and more stable than the TNM staging system.

In our method, we used consensus clustering to build a baseline model and applied a support vector machine to classify new samples. It was known that for some clustering methods, the clustering results depended on the initializations. For example, the results of K-means clustering depended on

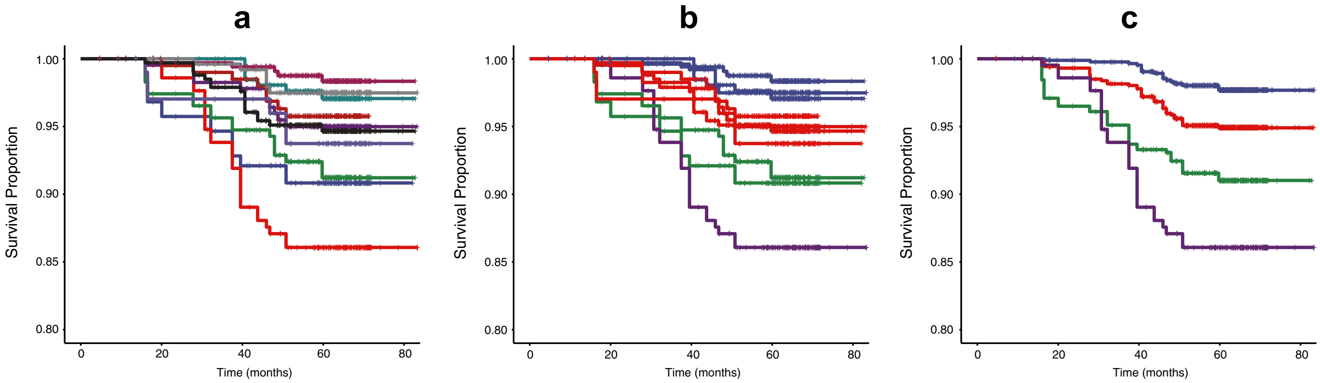
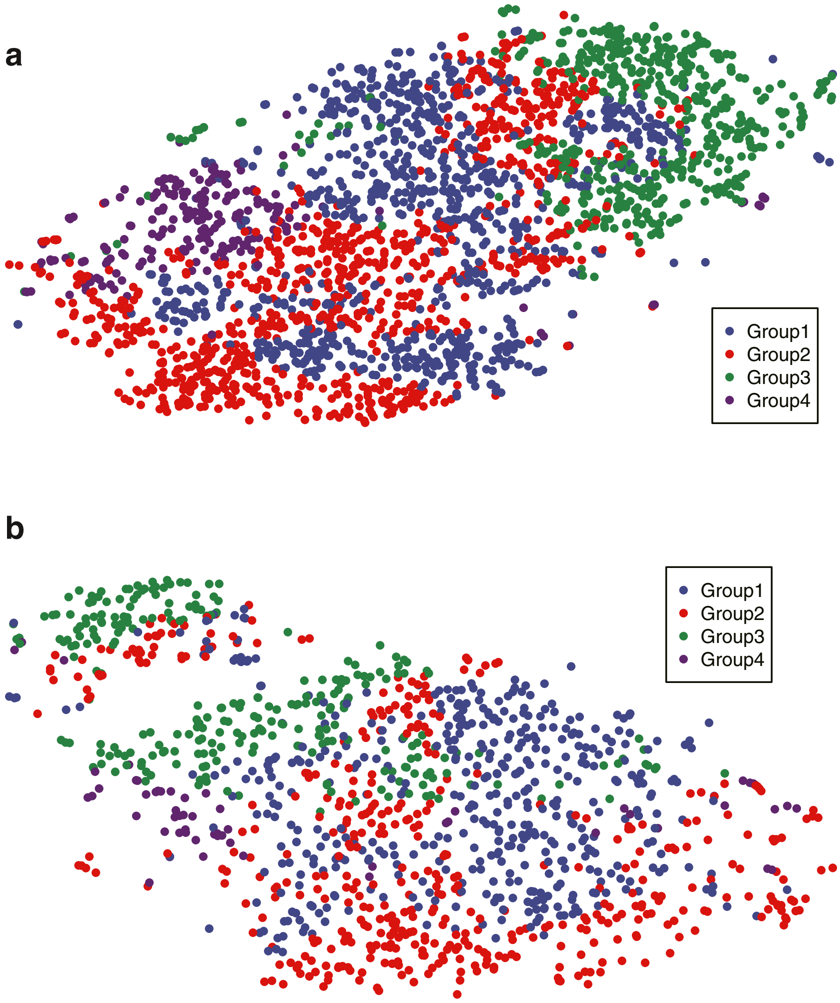


Fig. 2 Aggregation of subgroups with similar survival pattern. **a** Subgroups obtained from clustering. **b** Subgroups regrouping with similar survival. **c** Aggregation results

the setting of initial centers in spite of the same *K* value. Consensus clustering, or ensemble clustering, combined different clustering results to give a consensus one that was more reliable. The basic clustering method of the consensus clustering in this study could be replaced by other clustering methods such as spectral clustering, and the entropy-based consensus clustering method could also be substituted by other ensemble clustering algorithms.

As for the classification problem, we obtained the classification reference by clustering and the samples within the same class would be well clustered. Thus, most of the supervised machine learning algorithms, such as logistic regression and

Fig. 3 Visualization of radiomics features. **a** Training cohort. **b** Validation cohort



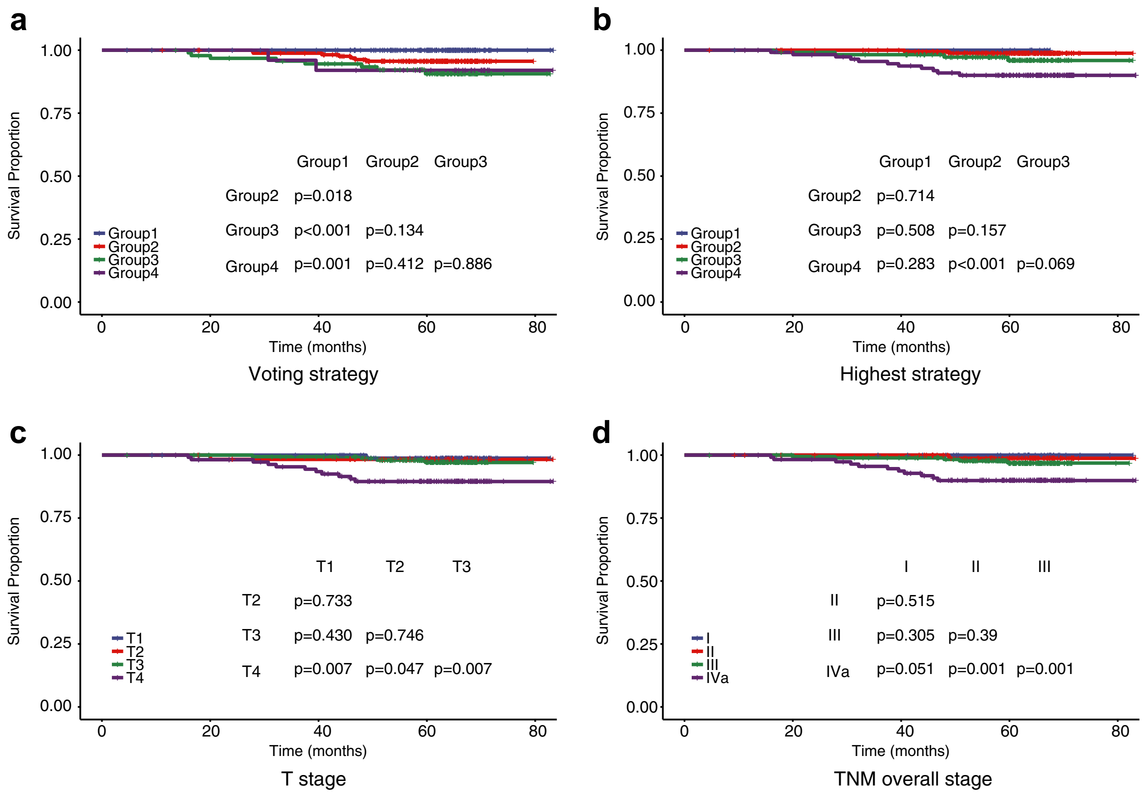


Fig. 4 Kaplan-Meier curves and log-rank test for different stratification methods for patients in the training cohort. **a** Voting strategy. **b** Highest strategy. **c** T-stage. **d** TNM overall stage

random forest, would perform well and could be the alternatives for SVM. We used SVM since it was robust and had an easy-to-apply kernel function.

It was important to note that we obtained more clusters than required in the clustering step, followed by an aggregation step. In fact, we found that if a small number of subgroups were directly obtained by the clustering step, there would be little significant difference between them. This might be on account of the discontinuous distribution of the features with a similar survival pattern in the feature space.

In the validation cohort, we also found that different slices on the same tumor often belonged to different subgroups, thereby indicating that different parts of a tumor may include different prognostic information because of intratumor heterogeneity. From the perspective of the tumor entity, the voting strategy and the highest strategy represent global information and local information in the tumor respectively. Our results demonstrated that the highest strategy performed better than the voting strategy, indicating that a patient's prognosis may depend on the most serious part of the tumor, rather than on the whole tumor. This finding also suggested that our slice-wise method could be used in the matter of selecting one of the MRI slices as a standard or representative one for further research.

The 8th edition of the UICC/AJCC staging system [22] and the Chinese 2008 staging system [23] are presently universally accepted. Recently, it was reported that the current 8th edition is imperfect because of a lack of separation between T2 and T3 NPC and stage II and III NPC [24]. Min Kang et al [25] found that the differences in LRFS (locoregional recurrence-free survival) rates between T1, T2, and T3 patients were not significant according to the 8th edition of the UICC/AJCC staging system, indicating that the hazard discrimination across T1–T3 patients was diminished. It seems necessary to explore more effective tools to optimize T category classification. In this current study, we found that the slice-wise approach for MR-based radiomics showed a better prognostic performance than the T-stage groupings. Our approach separated patients and demonstrated significant differences between the four groups, which may help to precisely stratify patients for individual therapeutic strategies in clinical practice, and thereby improve the clinical outcomes of patients with NPC.

In recent years, the potential value of radiomics approaches for achieving personalized medicine for different diseases such as cancer has been demonstrated. Radiomics converts imaging data into a high-dimensional mineable feature space using a large number of automatically extracted data-characterization algorithms [26]. Most studies applying radiomics approaches to cancer have only extracted features from the ROI representing the primary tumor, without considering ROIs of other metastatic lesions. For example, the potential of CT-

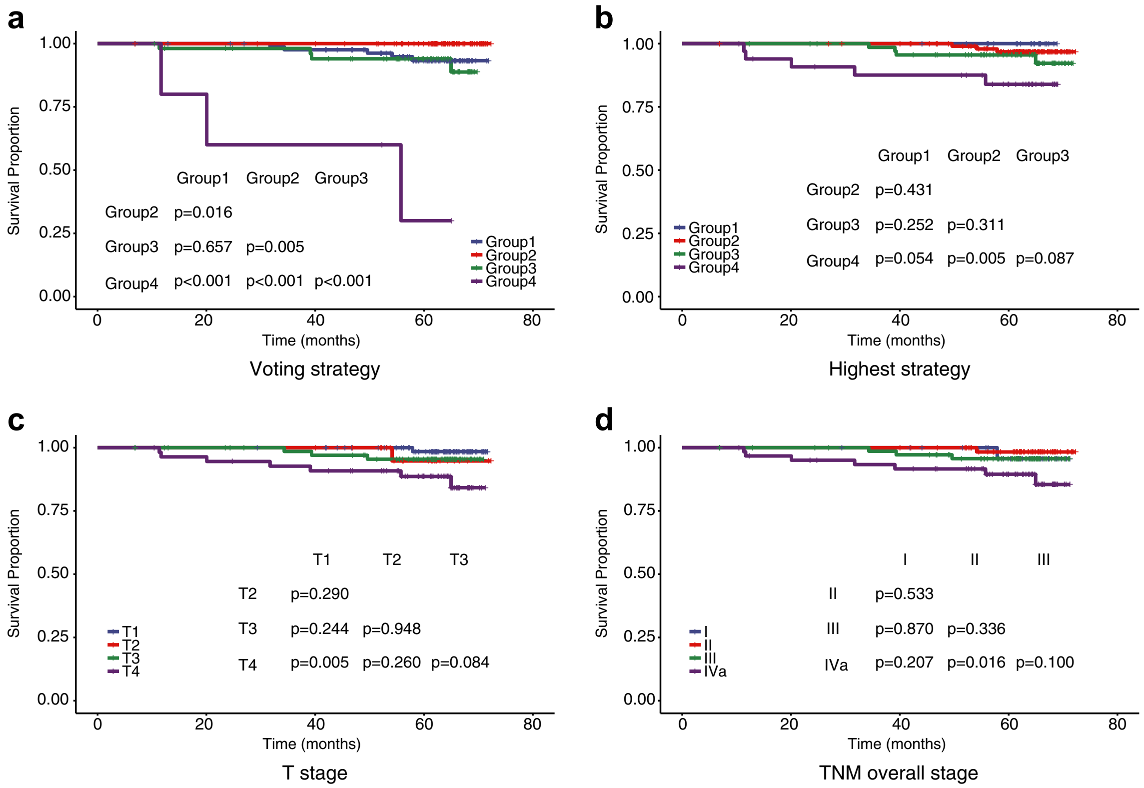


Fig. 5 Kaplan-Meier curves and log-rank test for different stratification methods for patients in the validation cohort. **a** Voting strategy. **b** Highest strategy. **c** T-stage. **d** TNM overall stage

based radiomics signatures for differentiating Borrmann type IV gastric cancer (GC) from primary gastric lymphoma (PGL) was evaluated on the basis of the entire primary tumor [27], and a radiomics nomogram was successfully constructed from the ROIs of primary tumors to stratify patients with early-stage non-small cell lung cancer [28]. Consistent with these previous studies, our results showed that MR-based radiomics of the primary tumor are capable of stratifying patients with non-metastatic NPC and predicting their survival. There are currently several reports that have demonstrated that MR-based radiomics models are of great value for determining the prognosis in NPC [16–20]. Nonetheless, these studies are subject to limitations. First, they focused more on advanced nasopharyngeal carcinoma cohorts, with the cases not being consecutive. In the clinical situation, it is more difficult to evaluate the prognosis of consecutive patients. Second, the patients enrolled in their cohorts were not all treated with IMRT, which is currently the standard treatment. Therefore, to address these problems, our study recruited patients treated with IMRT in all clinical stages of non-metastatic NPC. Thus, the prognostic predictive model we developed is up to date with respect to the development of treatment techniques in this area and should be more credible and accurate.

Table 2 Differences between C-indices of different methods

p value	Highest	Voting	*T*	TNM
Highest	/	/	0.567	0.735
Voting	/	/	0.103	0.177
T	0.571	0.554	/	/
TNM	0.408	0.717	/	/

The left lower part shows the *p* value in the training cohort; the right upper part shows the *p* value in the validation cohort

There were several limitations to our study. First, this study was limited by the incidence rate of events in the cohort. To alleviate the skewness of the dataset, we did not exclude the event patients with a short follow-up. Second, feature selection was not implemented owing to the uncertain nature of feature selection methods in high-dimensional data. It was still a challenge to select contributing features in a high-dimensional context since the high dimension would lead to various problems, such as noninvertible covariance matrices and random feature selection. We did apply a LASSO-COX model and selected features most of which were sparse histogram features. This was caused by the unstable nature of LASSO problem in high-dimensional problems. Little improvement turned out from the resulting model and we considered that the selected features made little sense. Third, the information of lymph nodes was not included since we aimed to explore the prognostic ability of radiomics features of primary tumors. Further researches involving lymph nodes would be carried out in the future. Fourth, we focused on non-metastatic NPC and excluded metastatic ones. It was undeniable that metastasis did affect survival, but this was not the only factor that led to a bad prognosis. Our study focused on the survival mostly affected by the primary tumor. In addition, patients with metastasis usually need different treatments from non-metastatic ones and the failures of metastatic patients were caused by various reasons. We considered these as uncertain factors that would affect the experiment results and thus excluded the metastatic patients. Fifth, genomic data, laboratory examination results, and other information should be added to the analysis process in future work to enhance performance. Finally, we did not perform reproducibility analysis for radiomics features since our ROIs were segmented with full consents by four radiologists and we applied the active contour model. The ROIs were confirmed and unique. We considered it an important limitation in our study and it would enrich the analysis in our further studies.

As for the generalization ability, we thought that our slice-wise analysis method could be used in many other imaging and diseases to explore the feasibility of radiomics for the purpose of prognosis or diagnosis. This method could be applied to both single modality imaging data and aligned multiple modality imaging data. For multiple modality imaging data that were not aligned, it could be applied by building a model for each modality and combining all models to perform an analysis.

In summary, this study exploited and validated that MRI-based radiomics features were capable of stratifying patients with non-metastatic NPC into subtypes with distinct survival patterns. The results using MRI-based radiomics features showed a superior performance better over the T staging, competitive to and more stable than the TNM staging system.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hong-min Cai.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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