Radiomics signature of computed tomography imaging for prediction of survival and chemotherapeutic benefits in gastric cancer

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ABSTRACT

To develop and validate a radiomics signature for the prediction of gastric cancer (GC) survival and chemotherapeutic benefits. In this multicenter retrospective analysis, we analyzed the radiomics features of portal venous-phase computed tomography in 1591 consecutive patients. A radiomics signature was generated by using the Lasso-Cox regression model in 228 patients and validated in internal and external validation cohorts. Radiomics nomograms integrating the radiomics signature were constructed, demonstrating the incremental value of the radiomics signature to the traditional staging system for individualized survival estimation. The performance of the nomograms was assessed with respect to calibration, discrimination, and clinical usefulness. The radiomics signature consisted of 19 selected features and was significantly associated with DFS (disease-free survival) and OS (overall survival). Multivariate analysis demonstrated that the radiomics signature was an independent prognostic factor. Incorporating the radiomics signature into the radiomics-based nomograms resulted in better performance for the estimation of DFS and OS than the clinicopathological nomograms and TNM staging system, with improved accuracy of the classification of survival outcomes. Further analysis showed that stage II and III patients with higher radiomics scores exhibited a favorable response to chemotherapy. In conclusion, the newly developed radiomics signature is a powerful predictor of DFS and OS, and it may predict which patients with stage II and III GC benefit from chemotherapy.

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1. Introduction

Gastric cancer (GC) is the fifth most common human malignant disease and the third leading cause of cancer-related death worldwide. [44] Staging according to the TNM (tumor, node, and metastasis) system and histological subtype has been the most commonly used benchmark for the prognostic definition and establishment of treatment strategy in GC. According to the new US National Comprehensive Cancer Network guidelines, patients with advanced GC are recommended to receive chemotherapy.([5]; Group et al., [15]; [36]) However, large variations in clinical outcomes have been shown in patients with the same stage and similar treatment regimens. [5,22,36,41] These findings suggest that the present GC staging system provides inadequate prognostic information and does not reflect the biological heterogeneity of GC.
Radiomics is an emerging field that converts imaging data into a high-dimensional mineable feature space using a large number of automatically applied data-characterization algorithms. [1,13] By extracting large data sets of quantitative descriptors from routinely acquired computed tomography (CT) studies in a high-throughput manner, radiomics enables the noninvasive profiling of tumor heterogeneity.

[1,8,13,37] Recent advances in radiomics have provided insights for personalized medicine in oncological practice associated with tumor detection, prognosis, subtype classification, lymph node metastasis, distant metastasis, and therapeutic response evaluation. [1–3,8,13,19,20] However, research of radiomics with respect to GC survival and chemotherapeutic benefits is still lacking.

The combined analysis of a panel of biomarkers as a signature, rather than individual analyses, is the approach that shows the most promise to change clinical management. [19,20,50,52] The least absolute shrinkage and selection operator (LASSO) method is a popular method for regression of high-dimensional predictors. [42,43,52] Using the LASSO Cox regression model, we previously constructed an immune signature that could effectively predict recurrence, disease-free survival (DFS) and overall survival (OS) in GC. [25,49] Although CT texture assessments have been reported to be associated with prognosis in patients with GC, [12,51] to the best of our knowledge, an optimal approach that combines multiple imaging biomarkers as a predictive signature for survival and chemotherapeutic benefits has not yet been developed.

In this study, we developed and validated a multiple-feature-based radiomics signature to predict DFS and OS and assessed its incremental value to the traditional staging system and clinicopathological risk factors for individual DFS and OS estimation. Furthermore, the radiomics signature might be able to predict which patients with stage II and III GC benefit from adjuvant chemotherapy.
Table 1: Clinical characteristics of patients according to the radiomics score in the training and validation cohorts.

| Variables                      | Training cohort (n = 228) | Internal validation cohort (n = 186) | External validation cohort (n = 1177) |
|--------------------------------|---------------------------|-------------------------------------|--------------------------------------|
|                                | low-RS (%) | medium-RS (%) | high-RS (%) | p-value | low-RS (%) | medium-RS (%) | high-RS (%) | p-value | low-RS (%) | medium-RS (%) | high-RS (%) | p-value |
| Gender                         |             |               |             |         |             |               |             |         |             |               |             |         |
| Male                           | 77(40.0%)   | 30(34.4%)    | 34(60.0%)   | 0.817   |             |               |             |         |             |               |             | 0.001   |
| Female                         | 51(34.4%)   | 16(34.4%)    | 35(60.0%)   | 0.210   |             |               |             |         |             |               |             | 0.001   |
| Age(years)                     |             |               |             |         |             |               |             |         |             |               |             | 0.020   |
| <60                            | 88(60.3%)   | 28(19.2%)    | 30(20.5%)   | 0.019   |             |               |             |         | 269(40.1%) | 234(34.9%)    | 167(24.9%)  | 0.001   |
| ≥60                            | 40(48.8%)   | 18(22%)      | 24(29.3%)   | 0.968   |             |               |             |         |            |               |             |         |
| Charlson comorbidity index     |             |               |             |         |             |               |             |         |            |               |             |         |
| 0                              | 86(56.6%)   | 28(18.4%)    | 38(25%)     | 0.129   |             |               |             |         |            |               |             |         |
| 1                              | 34(35.7%)   | 15(26.4%)    | 12(19.7%)   | 0.060   |             |               |             |         |            |               |             |         |
| 2                              | 58(58.3%)   | 18(31.3%)    | 13(29.3%)   | 0.006   |             |               |             |         |            |               |             |         |
| 3                              | 1(33.3%)    | 2(66.7%)     | 0(0%)       | 0.001   |             |               |             |         |            |               |             |         |
| Tumor size(cm)                 |             |               |             |         |             |               |             |         |            |               |             |         |
| <4                             | 60(65.2%)   | 14(15.2%)    | 18(19.6%)   | 0.001   |             |               |             |         |            |               |             |         |
| ≥4                             | 68(50%)     | 32(23.5%)    | 36(26.5%)   | 0.266   |             |               |             |         |            |               |             |         |
| Cardia                         | 29(69%)     | 6(14.3%)     | 7(16.7%)    | 0.015   |             |               |             |         |            |               |             |         |
| Body                           | 28(66.7%)   | 6(14.3%)     | 8(19%)      | 0.015   |             |               |             |         |            |               |             | 0.066   |
| Antrum                         | 55(49.1%)   | 26(23.2%)    | 31(27.7%)   | 0.103   |             |               |             |         |            |               |             |         |
| Whole                          | 16(50%)     | 8(25%)       | 8(25%)      | 0.001   |             |               |             |         |            |               |             |         |
| Differentiation                |             |               |             |         |             |               |             |         |            |               |             |         |
| Well                            | 23(82.1%)   | 3(10.7%)     | 2(7.1%)     | 0.001   |             |               |             |         |            |               |             |         |
| Moderate                       | 55(88.8%)   | 13(16.3%)    | 12(15%)     | 0.001   |             |               |             |         |            |               |             |         |
| Poor and undifferentiated      | 50(41.7%)   | 22(18.3%)    | 26(21.3%)   | 0.001   |             |               |             |         |            |               |             |         |
| Lauren type                    |             |               |             |         |             |               |             |         |            |               |             |         |
| Intestinal type                | 80(71.4%)   | 12(10.7%)    | 10(9%)      | 0.142   |             |               |             |         |            |               |             |         |
| Diffuse or mixed               | 48(41.4%)   | 34(29.3%)    | 34(29.3%)   | 0.001   |             |               |             |         |            |               |             |         |
| CEA                            |             |               |             |         |             |               |             |         |            |               |             |         |
| Elevated                       | 11(33.3%)   | 10(33.3%)    | 10(33.3%)   | 0.005   |             |               |             |         |            |               |             |         |
| Normal                         | 117(60%)    | 34(17.4%)    | 44(22.6%)   | 0.001   |             |               |             |         |            |               |             |         |
| CA199                          |             |               |             |         |             |               |             |         |            |               |             |         |
| Elevated                       | 20(35.7%)   | 12(21.4%)    | 24(42.9%)   | 0.001   |             |               |             |         |            |               |             |         |
| Normal                         | 108(62.8%)  | 34(19.8%)    | 30(17.4%)   | 0.001   |             |               |             |         |            |               |             |         |
| Depth of invasion              |             |               |             |         |             |               |             |         |            |               |             |         |
| T1                             | 16(100%)    | 0(0%)        | 0(0%)       | 0.001   |             |               |             |         |            |               |             |         |
| T2                             | 12(75%)     | 4(25%)       | 0(0%)       | 0.001   |             |               |             |         |            |               |             |         |
| T3                             | 3(42.9%)    | 0(0%)        | 12(17.1%)   | 0.001   |             |               |             |         |            |               |             |         |
| T4                              | 75(65.2%)  | 22(19.1%)    | 18(15.7%)   | 0.001   |             |               |             |         |            |               |             |         |
| Lymph node metastasis          |             |               |             |         |             |               |             |         |            |               |             |         |
| N0                             | 32(71.1%)   | 11(24.4%)    | 2(4.4%)     | 0.001   |             |               |             |         |            |               |             |         |
| N1                             | 27(75%)     | 5(13.9%)     | 4(11.1%)    | 0.001   |             |               |             |         |            |               |             |         |
| N2                             | 37(55.2%)   | 10(14.9%)    | 20(29.9%)   | 0.001   |             |               |             |         |            |               |             |         |
| N3                             | 32(40%)     | 20(25%)      | 28(35%)     | 0.001   |             |               |             |         |            |               |             |         |
| Distant metastasis             |             |               |             |         |             |               |             |         |            |               |             |         |
| M0                             | 120(66.3%)  | 30(16.6%)    | 31(17.1%)   | 0.004   |             |               |             |         |            |               |             |         |
| M1                             | 8(17%)      | 16(34%)      | 23(49%)     | 0.001   |             |               |             |         |            |               |             |         |

RS: radiomic score.
first. The OS was defined from the date of surgery to the date of all-cause death or the latest follow-up used for censoring.

2.6. Statistical analysis

Differences in distributions between the variables examined were assessed with the unpaired, 2-tailed $\chi^2$ test or the Fisher exact test as appropriate. The Kaplan-Meier method and log-rank test were used to estimate DFS and OS. Multivariate analyses were performed using the Cox proportional hazards model. Statistical analysis was conducted with R software (version 3.1.0) and SPSS software (version 19.0). Bonferroni correction was applied to obtain the corrected $P$ value for multiple comparisons. The packages in R that were used in this study are reported in Supplementary Materials. A two-sided $P$ value $< 0.05$ was considered significant.

3. Results

The clinicopathological characteristics for the training cohort, internal validation cohort and external validation cohort are listed in Table 1. Of the 1591 patients included in the study, 1081 (67.9%) were men, and the median (interquartile range [IQR]) age of all patients was 57 (49–65) years. In the training cohort, the median (IQR) survival time for DFS and OS were 29 (6–70) and 45 (11–74) months, respectively. In the internal validation cohort, the median (IQR) survival times for DFS and OS were 31 (9–48) and 39 (17.0–51.25) months, respectively, and in the external validation cohort, the median (IQR) survival times for DFS and OS were 36.87 (20.32–55.79) and 38.03 (22.9–56.07) months, respectively.

The inter and intraobserver reproducibility of the texture feature extraction was high (Supplementary Materials). Therefore, all outcomes were based on the measurements of the first radiologist.

134. Construction of the radiomics score-based radiomics signature

A LASSO Cox regression model was used to build a prognostic classifier, which selected 19 potential predictors from the 269 features identified in the training cohort (Fig. S3). The radiomics signature was constructed, including a radiomics score calculation formula (Supplementary Materials). The optimum cutoffs generated by the X-tile plot were $-1.1$ and $-0.8$ (Fig. S4). Accordingly, patients were classified into a low-radiomics score group (radiomics score $< -1.1$), a medium-radiomics score group ($-1.1 \leq$ radiomics score $< -0.8$), and a high-radiomics score group (radiomics score $\geq -0.8$). We assessed the prognostic accuracy of the radiomics score in the training cohort using time-dependent receiver operator characteristics (ROC) analysis at different follow-up times (Fig. 1A). The 5-year DFS and OS were 59.4% and 67.2%, respectively, for the low-radiomics score group; 13.0% and 17.4%, respectively, for the medium-radiomics score group; and both 0 for the high radiomics score group (hazard ratios[HRs]) 2.980 (2.421–3.669) and 3.722(2.964–4.673), respectively; all $P < 0.001$ and corrected $P < 0.001$; Fig. 1A). We then performed the same analyses (time-dependent ROC analysis and Kaplan-Meier survival analysis) in the internal validation cohort and similar results were observed (HR 3.137 (2.493–3.947) and 3.415(2.691–4.333), respectively; all $P < 0.001$ and corrected $P < 0.001$; Fig. 1B). To confirm that the radiomics signature had an excellent prognostic value in different populations, we further applied it to the external validation cohort, and found similar results (Fig. 1C). When the patients were stratified by clinicopathological risk factors, the radiomics signature remained a clinically and statistically significant prognostic predictor (Fig. S5–S8).

We also assessed the distribution of radiomics scores, recurrence and survival statuses as well as the expression of 19 radiomics features in the internal and external cohorts (Fig. S9–S10). Patients with higher radiomics scores were more likely to have recurrences and deaths. In univariable analysis, low radiomics score patients were associated with significantly poorer OS and DFS (Table S1). Variables demonstrating a significant effect on OS and DFS were included in the multivariable analysis. Multivariate Cox regression analysis after
Fig. 1. Radiomics score measured by time-dependent ROC curves and Kaplan-Meier survival in the training, internal and external validation cohorts. (A) Training cohort. (B) Internal validation cohort. (C) External validation cohort. We used AUCs at 1, 3, and 5 years to assess prognostic accuracy in the training and validation cohorts. We calculated $P$-values using the log-rank test. Data are the AUC or $P$-value. ROC = receiver operator characteristic. AUC = area under the curve. HR = hazard ratio.
Radiomics score patients with stage II and III GC could benefit from postoperative adjuvant chemotherapy. A test for an interaction between radiomics score and adjuvant chemotherapy indicated that the benefit from adjuvant chemotherapy was superior among patients with high radiomics scores (internal cohort: OS, HR 0.148 (0.066–0.333), \(P < 0.001\) and corrected \(P < 0.001\); DFS, 0.176 (0.083–0.374), \(P < 0.001\) and corrected \(P < 0.001\); and external cohort: OS, HR 0.394 (0.293–0.529), \(P < 0.001\) and corrected \(P < 0.001\); DFS, 0.412 (0.306–0.554), \(P < 0.001\) and corrected \(P < 0.001\); all \(P < 0.0001\) for interaction; Table 3) than among those with low and medium scores. The corresponding Kaplan-Meier survival curves, which comprehensively compared low, medium, with high radiomics score by treatment, are shown in Fig. 5. The results from the subset analysis using radiomics score classifier revealed that chemotherapy significantly increased DFS and OS in the high-radiomics score group (internal cohort: \(P < 0.001\) and corrected \(P < 0.001\); DFS, 0.176 (0.083–0.374), \(P < 0.001\) and corrected \(P < 0.001\); and external cohort: \(P < 0.001\) and corrected \(P < 0.001\); \(P < 0.001\); respectively), but had no significant effect in the low-radiomics score group (internal cohort: \(P = 0.510\) and corrected \(P = 1.000\), \(P = 0.345\) and corrected \(P = 0.999\); and external cohort: \(P = 0.325\) and corrected \(P = 0.975\), \(P = 0.384\) and corrected \(P = 0.999\); respectively; Fig. 5). Patients with medium radiomics scores also obtained a survival benefit from chemotherapy, although not significantly in the internal cohort (internal cohort: \(P = 0.062\) and corrected \(P = 0.186\), \(P = 0.292\) and corrected \(P = 0.876\); and external cohort: \(P = 0.002\) and corrected \(P = 0.006\), \(P = 0.004\) and corrected \(P = 0.012\); respectively). Furthermore, when the patients were stratified by clinicopathological risk factors, similar results were also observed (Fig. S14–15). Consequently, these results suggested that the radiomics score could successfully identify patients with stage II and III GC who are suitable candidates for chemotherapy.

### 4. Discussion

This study extends the analysis of individual imaging features to an “-omics”-based approach for survival estimation. A multiple-feature-based radiomics signature was identified to be an independent prognostic factor in patients with GC. The radiomics signature successfully stratified those patients into high-, medium-, and low-radiomics score groups with significant differences in DFS and OS. The radiomics nomograms performed better than the traditional staging system and clinicopathological nomograms, demonstrating well the incremental value of the radiomics signature for individualized DFS and OS estimation.
The present radiomics signature, consisting of 19 texture features, provides a noninvasive, fast, low-cost and reproducible method for obtaining phenotypic information, potentially accelerating the development of personalized medicine. The findings from previous studies have supported the hypothesis that phenotypic and proteogenomic information of the tumor can be deduced from radiomics analysis.

Fig. 2. Kaplan-Meier survival analysis of disease-free survival and overall survival according to the radiomics score classifier in subgroups of GC patients in the total internal and external cohorts. Total internal cohort (left pane): (A) Stage I (n = 38). (B) Stage II (n = 59). (C) Stage III (n = 234). (D) Stage IV (n = 83). External cohort (right pane): (A) Stage I (n = 206). (B) Stage II (n = 299). (C) Stage III (n = 555). (D) Stage IV (n = 117).
### Table 1: Radiomics Score and Clinical Parameters

| Parameter                      | Group 1 | Group 2 |
|-------------------------------|---------|---------|
| Distant metastasis            | 15      | 8       |
| Depth of invasion             | 26      | 20      |
| CA 159                       | 12      | 14      |
| Lymph node metastasis        | 16      | 18      |
| Diffusion                   | 0.5     | 0.7     |
| Radiomics score              | 0.2     | 0.3     |

### Radiomics Nomogram for DFS

- **Training cohort**
  - 1-year survival: 0.8, 0.7, 0.6, 0.5, 0.4
  - 5-year survival: 0.4, 0.3, 0.2, 0.1

- **Internal validation cohort**
  - 1-year survival: 0.8, 0.7, 0.6, 0.5, 0.4
  - 5-year survival: 0.4, 0.3, 0.2, 0.1

- **External validation cohort**
  - 1-year survival: 0.8, 0.7, 0.6, 0.5, 0.4
  - 5-year survival: 0.4, 0.3, 0.2, 0.1

### Radiomics Nomogram for OS

- **Training cohort**
  - 1-year OS: 0.8, 0.7, 0.6, 0.5, 0.4
  - 3-year OS: 0.4, 0.3, 0.2, 0.1
  - 5-year OS: 0.2, 0.1

- **Internal validation cohort**
  - 1-year OS: 0.8, 0.7, 0.6, 0.5, 0.4
  - 3-year OS: 0.4, 0.3, 0.2, 0.1
  - 5-year OS: 0.2, 0.1

- **External validation cohort**
  - 1-year OS: 0.8, 0.7, 0.6, 0.5, 0.4
  - 3-year OS: 0.4, 0.3, 0.2, 0.1
  - 5-year OS: 0.2, 0.1
for more precise therapeutic care. 

Op imaging biomarkers incorporating phenotypic and genotypic metrics in radiogenomics is needed to elucidate the relationship between tumor biology in its entirety, including capturing the intrinsic tumor heterogeneity in a noninvasive method. In oncology, it remains an intractable challenge. On the one hand, the biological processes involve multiple interacting components. On the other hand, it is difficult to correlate a single radiomics-based factor with a pathophysiological basis in an intuitive method. Therefore, the construction of multifactor panels is a more common approach for outcome estimation in the “-omics” setting. Radiomics refers to the comprehensive quantification of tumor phenotypes by applying a large number of quantitative image features. According to the radiomics hypothesis, the genomic heterogeneity may translate to expression in an intratumoral heterogeneity that can be assessed through imaging and that would ultimately exhibit worse prognosis. 

The radiogenomics analysis by Aerts et al. revealed that a prognostic radiomic signature, capturing intratumour heterogeneity, is associated with underlying gene expression patterns. As demonstrated in the present study, the multifeature radiomics signature effectively predicts survival outcomes, which also supports the hypothesis that the radiomics signature has the potential to capture intratumoral heterogeneity in a noninvasive method. In oncology, radiogenomics enable a deeper characterization and understanding of tumor biology in its entirety, including capturing the intrinsic tumor heterogeneity that can drive tumor development. Further effort in radiogenomics is needed to elucidate the relationship between tumor genomics characteristics and their imaging appearance as well as developing imaging biomarkers incorporating phenotypic and genotypic metrics that can predict risk and outcomes, thereby better stratifying patients for more precise therapeutic care. 

The complex nature and biological processes of malignancy involve multiple interacting components, which may be better reflected when one takes into account the interactions between different features. As the first attempt, to the best of our knowledge, to address the issue of survival estimation using a multicomponent radiomics signature in GC, our study supported the suggestion that multiple variables could provide a more statistically robust approach. Although the selected 19 features were observed to be associated with DFS and OS (Figs. S16–17), the radiomics signature developed by the Lasso-Cox regression model showed better prognostic value than any single feature (Fig. S18).

Current guidelines recommend chemotherapy as a standard component for advanced GC therapies, whereas existing studies have shown that a subgroup of patients does not benefit from present chemotherapy strategies. Thus, the accurate identification of subgroups of patients will improve the prognostic system and lead to more personalized therapy. A few studies have assessed the potential of texture analysis for treatment response assessment. Ahn et al. showed that CT texture analysis is useful for the prediction of therapeutic response after cytotoxic chemotherapy in patients with liver metastasis from colorectal cancer. 

Yoon et al. reported that heterogeneous texture features on CT images are associated with better survival in patients with HER2-positive advanced gastric cancer who received trastuzumab-based treatment. In the present study, we showed that chemotherapy provides a better survival benefit to stage II and III GC patients classified as high radiomics score and that further use of the radiomics score enables a more accurate identification of patients who might benefit from chemotherapy. For patients with low radiomics scores, more effective systemic approaches to improve treatment outcomes need to be identified. Thus, the radiomics score is both a prognostic and predictive tool in stage II and III disease. Thus, patients with higher radiomics scores have a greater likelihood of recurrence and a clear benefit from chemotherapy. The mechanism of the relationship between radiomic features and chemotherapy has not been shown thoroughly, but it may be associated with the strong correlation between intratumor heterogeneity radiomic features and cell cycling pathways, and further radiogenomics studies may provide additional information and strategies for treatment.

TNM staging is the most commonly used system to predict outcome for GC patients. However, patients within the same stage show different genetic, cellular, and clinicopathological characteristics, and their survival is not uniform. As shown in the present study, the radiomics signature successfully identified high-risk patients with poor survival outcomes within stages II, III, and IV, for whom more intensified treatment was needed. These results suggested that the radiomics signature reinforced the prognostic ability of TNM stage, thereby adding prognostic value to TNM staging. To provide a more individualized staging system, nomograms have been developed to evaluate a large number of significant clinicopathological predictors to better predict the prognosis of individual patients. The improved prediction of individual outcomes would be useful for counselling patients, personalizing treatment, and scheduling patients’ follow-ups. Although there are several GC nomograms available, no particular nomogram has been used widely in clinical settings. In the present study, we developed and validated two nomograms, which included the radiomics signature, differentiation and radiologic images. However, interpreting the complex associations between the biological processes and radiomic features still remains an intractable challenge. On the one hand, the biological processes involve multiple interacting components. On the other hand, it is difficult to correlate a single radiomics-based factor with a pathophysiological basis in an intuitive method. Therefore, the construction of multifactor panels is a more common approach for outcome estimation in the “-omics” setting. Radiomics refers to the comprehensive quantification of tumor phenotypes by applying a large number of quantitative image features. According to the radiomics hypothesis, the genomic heterogeneity may translate to expression in an intratumoral heterogeneity that can be assessed through imaging and that would ultimately exhibit worse prognosis.

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Current guidelines recommend chemotherapy as a standard component for advanced GC therapies, whereas existing studies have shown that a subgroup of patients does not benefit from present chemotherapy strategies. Thus, the accurate identification of subgroups of patients will improve the prognostic system and lead to more personalized therapy. A few studies have assessed the potential of texture analysis for treatment response assessment. Ahn et al. showed that CT texture analysis is useful for the prediction of therapeutic response after cytotoxic chemotherapy in patients with liver metastasis from colorectal cancer. 

Yoon et al. reported that heterogeneous texture features on CT images are associated with better survival in patients with HER2-positive advanced gastric cancer who received trastuzumab-based treatment. In the present study, we showed that chemotherapy provides a better survival benefit to stage II and III GC patients classified as high radiomics score and that further use of the radiomics score enables a more accurate identification of patients who might benefit from chemotherapy. For patients with low radiomics scores, more effective systemic approaches to improve treatment outcomes need to be identified. Thus, the radiomics score is both a prognostic and predictive tool in stage II and III disease. Thus, patients with higher radiomics scores have a greater likelihood of recurrence and a clear benefit from chemotherapy. The mechanism of the relationship between radiomic features and chemotherapy has not been shown thoroughly, but it may be associated with the strong correlation between intratumor heterogeneity radiomic features and cell cycling pathways, and further radiogenomics studies may provide additional information and strategies for treatment.

TNM staging is the most commonly used system to predict outcome for GC patients. However, patients within the same stage show different genetic, cellular, and clinicopathological characteristics, and their survival is not uniform. As shown in the present study, the radiomics signature successfully identified high-risk patients with poor survival outcomes within stages II, III, and IV, for whom more intensified treatment was needed. These results suggested that the radiomics signature reinforced the prognostic ability of TNM stage, thereby adding prognostic value to TNM staging. To provide a more individualized staging system, nomograms have been developed to evaluate a large number of significant clinicopathological predictors to better predict the prognosis of individual patients. The improved prediction of individual outcomes would be useful for counselling patients, personalizing treatment, and scheduling patients’ follow-ups. Although there are several GC nomograms available, no particular nomogram has been used widely in clinical settings. In the present study, we developed and validated two nomograms, which included the radiomics signature, differentiation strategies. Thus, the accurate identification of subgroups of patients will improve the prognostic system and lead to more personalized therapy. A few studies have assessed the potential of texture analysis for treatment response assessment. Ahn et al. showed that CT texture analysis is useful for the prediction of therapeutic response after cytotoxic chemotherapy in patients with liver metastasis from colorectal cancer. Yoon et al. reported that heterogeneous texture features on CT images are associated with better survival in patients with HER2-positive advanced gastric cancer who received trastuzumab-based treatment. In the present study, we showed that chemotherapy provides a better survival benefit to stage II and III GC patients classified as high radiomics score and that further use of the radiomics score enables a more accurate identification of patients who might benefit from chemotherapy. For patients with low radiomics scores, more effective systemic approaches to improve treatment outcomes need to be identified. Thus, the radiomics score is both a prognostic and predictive tool in stage II and III disease. Thus, patients with higher radiomics scores have a greater likelihood of recurrence and a clear benefit from chemotherapy. The mechanism of the relationship between radiomic features and chemotherapy has not been shown thoroughly, but it may be associated with the strong correlation between intratumor heterogeneity radiomic features and cell cycling pathways, and further radiogenomics studies may provide additional information and strategies for treatment.

TNM staging is the most commonly used system to predict outcome for GC patients. However, patients within the same stage show different genetic, cellular, and clinicopathological characteristics, and their survival is not uniform. (Cancer Genome Atlas Research, [7]; [33,41]) As shown in the present study, the radiomics signature successfully identified high-risk patients with poor survival outcomes within stages II, III, and IV, for whom more intensified treatment was needed. These results suggested that the radiomics signature reinforced the prognostic ability of TNM stage, thereby adding prognostic value to TNM staging. To provide a more individualized staging system, nomograms have been developed to evaluate a large number of significant clinicopathological predictors to better predict the prognosis of individual patients. The improved prediction of individual outcomes would be useful for counselling patients, personalizing treatment, and scheduling patients’ follow-ups. Although there are several GC nomograms available, no particular nomogram has been used widely in clinical settings. In the present study, we developed and validated two nomograms, which included the radiomics signature, differentiation...
status, T stage, N stage, M stage, and CA199 level, to improve the accuracy of prognosis for GC patients. These nomograms can be used to better predict an individual patient's probability of 1-, 3-, and 5-year DFS and OS. The nomograms performed well with a higher C-index and positive NRI ($P < 0.05$). The decision curve analysis demonstrated that the radiomics nomogram was superior to both the clinicopathological nomogram and TNM staging system across the majority of the range of reasonable threshold probabilities, which indicated that the radiomics signature added incremental value for individualized estimation. Compared to previous studies, the radiomics nomograms greatly improved accuracy by integrating the radiomics signature. However, the Bland-Altman type plots showed that the radiomics nomograms didn’t have an excellent predictive effect for actual survival <20 months (Fig. S11). It is unclear what is the reason for these large discrepancies for short survival times. One possible explanation is the difference in patient populations. The staging of short survival cases was generally later. These patients’ survival time was easily affected by the surrounding environment in China, such as treatment condition, the economy condition, and rural/urban. [22] For example, patients with stage III GC were more likely to obtain greater survival benefit from chemotherapy than stage I or II patients with relatively longer survival, and stage III patients were more likely to receive chemotherapy than stage II patients. [22,25] The discrepancies also suggested that a summary performance

![Decision curve analysis for each model in the training and validation cohorts. The y-axis measures the net benefit. The net benefit was calculated by summing the benefits (true positive results) and subtracting the harms (false positive results), weighting the latter by a factor related to the relative harm of an undetected cancer compared with the harm of unnecessary treatment. The radiomics model had the highest net benefit compared to both the other models and simple strategies such as follow-up of all patients (green line) or no patients (horizontal black line) across the full range of threshold probabilities at which a patient would choose to undergo imaging follow-up.](image-url)
metric like concordance does not tell the entire story, more reasonable methods for evaluation of prediction model need to be developed in future.

The limitations of the present study included the relatively small sample size, and the retrospective nature of the data collection. Although the preferred design would be a prospective longitudinal cohort study, [34] the protracted length of a prospective longitudinal cohort study in GC (on account of the long wait required for survival outcomes) may make the study daunting. [36] Although a large-scale independent prospective multicenter validation cohort is warranted to evaluate the generalizability of the results, the decision curve analysis used in this study, which enables the evaluation of clinical relevance without the necessity for additional validation data in a traditional decision analytic approach, [46,47] demonstrated that the radiomics signature and radiomics nomogram hold great potential for clinical application in postoperative outcome estimation. Furthermore, the use of adjuvant chemotherapy was not within a randomized comparison, and the decision to treat or not to treat patients after surgery was made by the patients and/or clinicians. Therefore, we will develop a multicenter, prospective study to validate these results in a larger population in the future. In addition, other predictive biomarkers may be included to improve the accuracy of the nomograms.

In summary, the radiomics signature can effectively predict survival and add prognostic value to the TNM staging system. Moreover, the radiomics signature may be a useful predictive tool to predict patient benefit from chemotherapy. In addition, the radiomics nomogram may serve as a potential tool to guide individual care.

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Fig. 5. Adjuvant chemotherapy benefit compared using disease-free survival (DFS) and overall survival (OS) for stage II and III gastric cancer patients in the total internal cohort and external cohort. Kaplan-Meier survival curves for patients with stage II and III gastric cancer in different subgroups, which were stratified by the receipt of adjuvant chemotherapy. Total internal cohort (N = 293): left pane; External cohort (N = 854): right pane.
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Appendix A. Supplementary data

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