Cone-beam computed-tomography-based delta-radiomic analysis for investigating prognostic power for esophageal squamous cell cancer patients undergoing concurrent chemoradiotherapy

Takahiro Nakamoto a,b,*, Hideomi Yamashita b, Haruka Jinnouchi b, Kanabu Nawa b, Toshikazu Imae b, Shigeharu Takenaka b, Atsushi Aoki b, Takeshi Ohta b, Sho Ozaki b,c, Yuki Nozawa b, Keiichi Nakagawa b

a Department of Biological Science and Engineering, Faculty of Health Sciences, Hokkaido University, N12-W5, Kita-ku, Sapporo, Hokkaido 060-0812, Japan
b Department of Radiology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
c Graduate School of Science and Technology, Hirosaki University, 3 Bunkyo, Hirosaki, Aomori 036-8561, Japan

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ABSTRACT

Purpose: To investigate the prognostic power of cone-beam computed-tomography (CBCT)-based delta-radiomics in esophageal squamous cell cancer (ESCC) patients treated with concurrent chemoradiotherapy (CCRT).

Methods: We collected data from 26 ESCC patients treated with CCRT. CBCT images acquired at five time points (1st–5th week) per patient during CCRT were used in this study. Radiomic features were extracted from the five CBCT images on the gross tumor volumes. Then, 17 delta-radiomic feature sets derived from five types of calculations were obtained for all the cases. Leave-one-out cross-validation was applied to investigate the prognostic power of CBCT-based delta-radiomic features. Feature selection and construction of a prediction model using Coxnet were performed using training samples. Then, the test sample was classified into high or low risk in each cross-validation fold. Survival analysis for the two groups were performed to evaluate the prognostic power of the extracted CBCT-based delta-radiomic features.

Results: Four delta-radiomic feature sets indicated significant differences between the high- and low-risk groups ($p < 0.05$). The highest C-index in the 17 delta-radiomic feature sets was 0.821 (95% confidence interval, 0.735–0.907). That feature set had $p$-value of the log-rank test and hazard ratio of 0.003 and 4.940 (95% confidence interval, 1.391–17.544), respectively.

Conclusions: We investigated the potential of using CBCT-based delta-radiomics for prognosis of ESCC patients treated with CCRT. It was demonstrated that delta-radiomic feature sets based on the absolute value of relative difference obtained from the early to the middle treatment stages have high prognostic power for ESCC.

1. Introduction

Esophageal cancer is a malignant neoplasm developed in the esophagus; it is the tenth most common type of cancer and sixth most common cause of cancer mortality worldwide [1]. In addition, squamous cell cancer is the most frequently diagnosed histological subtype, and it is related to risk factors such as smoking and alcohol consumption [2–4]. Surgery resection, endoscopic resection, radiotherapy, chemotherapy, and concurrent chemoradiotherapy (CCRT) are treatments selected depending on the clinical stage, tumor location, and patient’s condition [5,6]. CCRT is a reliable treatment option for inoperable patients and can help preserve the esophagus [7,8]. Prediction factors of prognosis and treatment response during CCRT for esophageal cancer have been investigated using various approaches [9–12].

Radiomics is an effective approach to investigate relationships between quantitative image features and both prognosis and treatment response during CCRT for esophageal cancer. The feasibility of radiomics for predicting the prognosis and treatment response of esophageal squamous cell cancer (ESCC) patients treated with CCRT has been demonstrated, and radiomic features have been extracted from computed tomography (CT) or positron emission tomography images acquired before treatment (i.e., snapshot images) [13–17]. Nowadays,
radiomics using time-dependent variabilities of imaging features, called delta-radiomics, has attracted research attention. A common concept in delta-radiomics is that the variability of radiomic features extracted from medical images acquired at various time points before, during, and after the treatment may allow to predict the treatment prognosis and outcomes [18–20]. In fact, the variability of features from pre- to post-treatment is typically considered in delta-radiomics [20]. Its usage is promoted because most cancer patients undergo imaging examinations during diagnosis and follow up. In radiotherapy, volumetric images are acquired daily or weekly by cone-beam CT (CBCT) incorporated with linear accelerators before treatment delivery to perform image-guided radiotherapy. Multiple imaging points in small intervals are generally available during radiotherapy. Therefore, CBCT-based delta-radiomics may enable the detection of fine changes in features, which can reflect treatment effects during radiotherapy and provide a strong prognostic power of patients’ prognoses and outcomes. The potential of CBCT-based delta-radiomics for predicting treatment prognosis and response has been investigated in lung, head and neck, and prostate cancers [21–25].

We hypothesized that delta-radiomic features of CBCT images from ESCC patients during treatment with CCRT can reflect treatment effects of both radiotherapy and chemotherapy regarding their prognosis and outcomes. Previous studies on CBCT-based delta-radiomics [21–25] individually defined calculations of delta-radiomic features. Therefore, various existing mathematical definitions of the delta-radiomic features should be compared to comprehensively investigate their prognostic power. Accordingly, we aimed to investigate the prognostic power of various CBCT-based delta-radiomic features for ESCC patients treated with CCRT. We considered the overall survival (OS) to evaluate the prognostic power in this study.

Fig. 1. Workflow of this study. (I) Data from 26 ESCC patients were retrospectively collected. (II) Volumes of interest (VOIs) on the planning CT images were aligned to the CBCT images using deformable image registration (DIR). (III) Delta-radiomic features were calculated from radiomic features in the VOIs on CBCT image series. (IV) LOOCV was applied to distinguish samples as having high or low risk using Coxnet-based prediction models. (V) Survival analysis was performed in stratified high- and low-risk groups to evaluate the prognostic power of delta-radiomic features.
2. Materials and methods

2.1. Study overview

Fig. 1 shows the overall workflow of this study. We collected ESCC patients’ OS information, radiation treatment planning CT images with tumor delineation, and CBCT images acquired just before treatment delivery and over 5 weeks. For each case, the tumor delineation on the planning CT image was aligned to five CBCT images using deformable image registration. Radiomic features were extracted from aligned tumor delineations on the five available CBCT images per patient. Then, delta-radiomic features were calculated across radiomic feature sets over 5 weeks for each case considering five types of calculations. We applied leave-one-out cross-validation (LOOCV) to investigate the prognostic power of the delta-radiomic features. Coxnet [26] was used to construct the prognostic model using training samples, and the test sample was classified into high or low risk based on a delta-radiomic score (Δrad-score) calculated from the delta-radiomic features and prognostic model, which indicates the OS event occurrence risk, per cross-validation fold. A dimensional selection of delta-radiomic features was performed before model construction. All the samples were stratified into high- and low-risk groups after LOOCV. Then, a survival analysis for the high- and low-risk groups was performed.

2.2. Clinical information

We obtained ethical approval for this study from our institutional review board (reference number: 3372). We retrospectively collected data from 117 first primary esophageal cancer patients treated with chemoradiotherapy from 2010 to 2016 in our hospital. The inclusion criterion was patients with ESCC treated with CCRT at a prescribed dose of 50.4 Gy/28 Fr (1.8 Gy/Fr). The exclusion criteria were the following: (i) data unavailable, (ii) not SCC or unknown histological subtype, (iii) not prescribed with 50.4 Gy/28 Fr, (iv) any treatment preformed prior to CCRT, (v) multiple primary gross tumor volumes, (vi) replanning during term of CCRT, and (vii) strict artifacts in CBCT images due to beam hardening or saturation dose in the CBCT imaging panel. Twenty-six patients who cleared the above exclusion criteria were enrolled in this study. Table 1 lists the clinical characteristics of the enrolled patients.

The radiation treatment plans of the 26 patients were designed by various radiation oncologists and medical physicists using a commercial radiation treatment planning system (Pinnacle versions 9.2–9.10, Philips Healthcare, Amsterdam, The Netherlands). Irradiation methods in the 26 patients included three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and combined 3D-CRT and IMRT. The treatments were delivered in accordance with the treatment plans by using commercial linear accelerators (Elekta Synergy, Elekta, Stockholm, Sweden). All patients underwent image-guided radiotherapy before beam delivery for treatment. The 26 patients underwent chemotherapy concurrently with radiotherapy. Cisplatin with 5-fluorouracil or nedaplatin with tegafur, gimeracil, and oteracil potassium, no. (%) 1 (3.8) Nedaplatin with tegafur, gimeracil, and oteracil potassium, no. (%) 25 (96.2) Median of OS, days (interquartile range) 1784 (738–2890) Number of censored cases, no. (%) 10 (38.5) volume CT dose index, scan collimation width, and image reconstruction algorithm for planning CT image acquisition were 20.90 mGy, 16 mm, and filtered back projection, respectively.

The CBCT images were acquired by a kilovoltage imaging system incorporated with a linear accelerator (X-ray volume imaging, Elekta) before radiotherapy. The tube voltage and tube current–time product, weighted CT dose index, and image reconstruction algorithm for CBCT image acquisition were 120 kV and 1.6 mAs, 15.85 mGy/rotation, and Feldkamp–Davis–Kress back projection, respectively. Medium and small collimators were used in the X-ray volume imaging system for image acquisition. The fields of view for the medium and small collimators were 270 mm and 410 mm, respectively. The X-ray irradiated length along the z-axis direction was 276.7 mm on the isocenter plane for both collimators. The acquisition intervals were approximately daily for IMRT and weekly for 3D-CRT. The treatment beams were delivered after modifying the patients’ positions by performing translation-based manual registration of the CBCT images to the planning CT images. We exported the registered CBCT images from the X-ray volume imaging system for analysis. Therefore, the matrix size, pixel size, and slice thickness of CBCT images were aligned to those of planning CT images.

The CBCT imaging intervals differed between IMRT and 3D-CRT. In the patients treated with IMRT, the CBCT images at approximately weekly intervals were selected for analysis. We used five CBCT images acquired at approximately weekly intervals over 5 weeks from the first day of treatment as the image series for all patients. The mean acquisition interval for all CBCT images used in the analysis was 6.9 days (range, 3–11 days).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Number of cases, no.</td>
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</tr>
<tr>
<td>Median of age, years (interquartile range)</td>
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<tr>
<td>Male, no. (%)</td>
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<td>Middle thoracic esophagus, no. (%)</td>
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<td>Lower thoracic esophagus, no. (%)</td>
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<td>Abdominal esophagus, no. (%)</td>
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<tr>
<td>Across locations, no. (%)</td>
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<tr>
<td>Clinical T stage</td>
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<tr>
<td>T1, no. (%)</td>
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<tr>
<td>T2, no. (%)</td>
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<tr>
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<td>6 (23.1)</td>
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<tr>
<td>N1, no. (%)</td>
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<tr>
<td>N2, no. (%)</td>
<td>4 (15.4)</td>
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<td>N3, no. (%)</td>
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<td>Clinical M stage</td>
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</tr>
<tr>
<td>Number of censored cases, no. (%)</td>
<td>10 (38.5)</td>
</tr>
</tbody>
</table>
2.4. Development environment

A commercial programming software tool (MATLAB version R2022b; MathWorks, Natick, MA, USA) was used for image preprocessing and extracting the radiomic features from the CBCT images. Open-source programming software tools (Python version 3.9 and R version 4.2) were used to calculate the delta-radiomic features and perform LOOCV, dimensional selection, Coxnet modeling and testing, and survival analysis. The programming software tools ran in a workstation equipped with a 2.1 GHz quad-core central processing unit (Intel Core i7-12700F; Intel, Santa Clara, CA, USA) and 32 GB of random-access memory. We used Ubuntu 22.04 Long Term Support running as a virtual machine on the Windows 10 operating system (Microsoft, Redmond, WA, USA).

2.5. Alignment of volumes of interest with CBCT images

Primary and nodal gross tumor volumes were manually delineated by a radiation oncologist on the planning CT image of each patient. We used the primary gross tumor volumes as volumes of interest (VOIs) for calculating radiomic features.

The VOIs on the planning CT images were aligned to those on the CBCT images in series. The VOIs were aligned by registering the CBCT images to the planning CT images using deformable image registration and then mapping the original VOIs on the deformed CBCT images. Therefore, a fixed VOI on the five deformed CBCT images was used for extracting the radiomic features in each case. Fig. 2 shows examples of a planning CT image with VOI, CBCT image, and deformed CBCT image with aligned VOI. Deformable image registration was performed using another commercial radiation treatment planning system (RayStation version 4.6; RaySearch Laboratories, Stockholm, Sweden) [27]. The accuracy and quality of deformable image registration between CT and CBCT images in the radiation treatment planning system were confirmed in [28,29].

2.6. Calculation of radiomic features

We performed image preprocessing following the guidelines of the Imaging Biomarker Standardisation Initiative [30,31] before calculating the radiomic features. The image preprocessing comprised (i) isotropic resampling of the CBCT image and VOI voxels, (ii) re-segmentation of VOIs, (iii) transformation of CBCT images using the wavelet transform and Laplacian of Gaussian filter, and (iv) quantization of image intensities. Details of image preprocessing are provided in Supplementary Sect. 1.

The radiomic features were calculated within the VOIs on the original image, wavelet images decomposed in eight sub-bands, and four Laplacian of Gaussian filtered images for all patients’ CBCT image series. We used the following radiomic feature families: (i) intensity histogram, (ii) gray-level co-occurrence matrix texture, (iii) gray-level run length matrix texture, (iv) gray-level size zone matrix texture, (v) neighboring gray-level dependence matrix texture, and (vi) neighborhood gray-tone difference matrix texture [30]. The number of radiomic features was 1131. Details of the radiomic feature calculations are provided in Supplementary Sect. 2, and the radiomic features and parameter settings for calculating the texture matrices are listed in Tables S1 and S2, respectively.

2.7. Calculation of delta-radiomic features

We calculated the quantitative variability over time of the features to extract delta-radiomic features from the CBCT image series. The delta-radiomic features were calculated for each of the 1131 radiomic features. We defined delta-radiomic features as four difference-based features and a gradient-based feature (GF).

The difference-based features described the variability in the radiomic features from the CBCT images of the first week to those of any other week. The difference-based features included absolute difference (AD), absolute value of absolute difference (AAD), relative difference (RD), and absolute value of relative difference (ARD), and they were defined as follows:

\[
AD_k = f_k - f_1, \quad (1)
\]

\[
AAD_k = |f_k - f_1|, \quad (2)
\]

\[
RD_k = \frac{f_k - f_1}{f_1}, \quad (3)
\]

\[
ARD_k = \left| \frac{f_k - f_1}{f_1} \right|, \quad (4)
\]

where \(k\), \(f_k\), and \(f_1\) are the week number and radiomic features extracted from a CBCT image in weeks \(k\) and 1, respectively. Eqs. (1) and (3) considered the orientation in variability, while Eqs. (2) and (4) disregarded orientation by using absolute values. The denominator in Eq. (3) should be the absolute value of \(f_1\) because some radiomic features could become negative (e.g., kurtosis and skewness in intensity histogram features).

The GF was the slope obtained from linear regression of the radiomic feature according to the acquisition week. The radiomic features across acquisition weeks were normalized with respect to the value from the first week, and the slope was then calculated by fitting using the linear least-squares method [21]. The scikit-learn library (version 0.24) in Python was used for calculating GF.

We defined 1131 delta-radiomic features calculated by the same method as a feature set, obtaining four difference-based feature sets for weeks 2–5 and one GF set. Therefore, 17 (=4 × 4 + 1) delta-radiomic feature sets were obtained. The delta-radiomic features were standardized to z-scores before analysis.

Fig. 2. Examples of (a) planning CT image (fixed image) with VOI, (b) CBCT image (moving image), and (c) deformed CBCT image with aligned VOI. The red regions indicate VOIs on the planning CT image and deformed CBCT image. Window widths/levels for visualization of the planning CT and CBCT images were adjusted to 300/50 Hounsfield units and 900/–350 Hounsfield units, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
2.8. LOOCV for evaluating prognostic power of delta-radiomic features

We used LOOCV for evaluating the prediction ability of delta-radiomic features owing to the small sample size. Fig. 3 shows the flowchart for evaluating the prognostic power of delta-radiomic features. First, the samples were split into one sample for testing and the remaining samples for training. Second, a dimensional selection of the delta-radiomic features and construction of a prognostic model were performed using the training samples. Finally, the test sample was classified into high or low risk using the trained model. This procedure was repeated until every sample was designated as the test sample (i.e., 26 iterations). Then, we performed a survival analysis for the high- and low-risk groups stratified in LOOCV. LOOCV and survival analysis were performed for each of the 17 delta-radiomic feature sets. The scikit-learn library was used for LOOCV.

2.9. Dimensional selection of delta-radiomic features

The delta-radiomic features were selected using training samples before constructing the prognostic model. We used two statistical filtering methods. Representative features for survival were identified by applying a two-sided log-rank test between high and low feature values. The cutoffs for the high and low values were the medians of the delta-radiomic features. We regarded features with \( p < 0.05 \) in the log-rank test as significantly representative features. Then, Spearman’s rank correlation coefficients were calculated for any combination of two representative features to find multicollinear features. We regarded a pair of representative features with \( |\rho| > 0.95 \) as multicollinear, and the feature of the pair with higher mean \( |\rho| \) with respect to the other features was removed [32]. The scikit-survival (version 0.16) and pandas (version 1.3) libraries in Python were used for the log-rank test and calculating Spearman’s rank correlation coefficients, respectively.

2.10. Prognostic model using Coxnet

A prognostic model was created using the training samples based on Coxnet, and the test sample was classified into high or low risk using the model in each fold of LOOCV (outer loop). Coxnet is a balance-regularized Cox regression using L1 and L2 norms [26]. We adopted Coxnet to avoid overfitting and underfitting to the few training samples. The Cox model consists of a baseline hazard function and a term describing the linear combination of coefficients as well as explanatory variables, and it is constructed by coefficient optimization [33]. In Coxnet, the coefficients are optimized by maximizing their partial likelihood with the L1 and L2 regularization terms. Parameters of regularization intensity \( \lambda \) and regularization balance \( \alpha \) between L1 and L2 norms were determined by grid search based on partial likelihood deviance with LOOCV (inner loop). We used the glmnet (version 4.1) and glmnetUtils (version 1.1) packages in R to construct the Coxnet model and determine its parameters. The searching range of \( \lambda \) was set to the default specification of glmnet, while that of \( \alpha \) was set to 0.0–1.0 in 0.1 increments. After training the Coxnet model, \( \Delta_{\text{rad-score}} \) values were calculated for the training and test samples. \( \Delta_{\text{rad-score}} \) for case \( n \) was defined as

\[
\Delta_{\text{rad-score}} = \hat{\beta}^T x_n
\]

where \( \hat{\beta} \) and \( x_n \) are column vectors of optimal coefficients and selected delta-radiomic features for case \( n \), respectively. \( \Delta_{\text{rad-score}} \) is equal to the natural logarithm of a ratio of the hazard function to the baseline hazard.

Fig. 3. Flowchart for evaluating prognostic power of the delta-radiomic features. The iterative process enclosed by the blue dashed box corresponds to LOOCV.
function. Therefore, a high $\Delta$ rad-score indicates a high event occurrence risk (poor prognosis). The test sample was classified into high or low risk based on $\Delta$ rad-score. We defined median of $\Delta$rad-score across training samples as a cutoff for classification of the test sample. If $\Delta$ rad-score of a test sample exceeded the cutoff, the sample was classified as indicating high risk; otherwise, it was classified as indicating low risk.

2.11. Survival analysis

We performed a survival analysis for the classified high- and low-risk groups in LOOCV. Kaplan–Meier curves were plotted to observe survival probabilities of the two groups. We used the ggplot2 (version 3.4) and survminer (version 0.4) packages in R for plotting the curves. A one-sided log-rank test was also performed to investigate the difference in survival probability between the high- and low-risk groups. The alternative hypothesis of the one-sided log-rank test was that survival probability in the low-risk group was larger than that in the high-risk group. The hazard ratios (HRs) from the high-risk group to the low-risk group were calculated by Cox regression to compare hazards in the high- and low-risk groups. Moreover, Harrell’s concordance indices (C-index) [34] of $\Delta$rad-score were calculated to evaluate the prognostic power of the delta-radiomic features. We used the nph (version 2.1), survival (version 3.2), and survcomp (version 1.48) packages in R for performing the one-sided log-rank test and calculating the HRs and C-indices, respectively. In the C-index, the nonparametric comparison proposed in [35] was performed between the delta-radiomic feature set with the highest C-index and the other feature sets to investigate significant differences in the C-indices. The comparison was performed using the compareC package (version 1.3) in R. We accepted the alternative hypotheses of the one-sided log-rank test and the test for comparing the C-indices at a 5% significance level ($p < 0.05$).

3. Results

Fig. 4 shows the Kaplan–Meier curves of the OS and risk tables for the high- and low-risk groups classified using all delta-radiomic feature sets in LOOCV. Table 2 lists the $p$-values of the log-rank test, HRs, and C-indices for all delta-radiomic feature sets in the survival analysis between the high- and low-risk groups as well as the $p$-values of the C-index. AAD$_2$, i.e., AAD delta-radiomic feature considering variability at week 3) with HR of 2.479 (95% confidence interval—CI, 0.839–7.326), ARD$_2$ with HR of 4.940 (95% CI, 1.391–17.544), ARD$_4$ with HR of 5.985 (95% CI, 1.646–21.767), and ARD$_4$ with HR of 3.122 (95% CI, 1.075–9.066) indicated significant differences in the log-rank test between the high- and low-risk groups ($p < 0.05$). Therefore, the survival curves of the high- and low-risk groups regarding AAD$_2$, ARD$_2$, ARD$_3$, and ARD$_4$ showed statistically significant differences, with the survival curves of the low-risk group being upper than those of the high-risk group. The 95% CI lower limits of the HRs in ARD$_2$, ARD$_3$, and ARD$_4$ exceeded 1. The delta-radiomic feature set with the highest C-index was ARD$_2$ with $p < 0.05$. However, no significant differences were observed between ARD$_2$ and both ARD$_3$ and ARD$_4$ with $p > 0.05$. Moreover, significant differences in C-index were observed between the feature set with the highest C-index in ARD (ARD$_2$) and that in AAD (AAD$_2$) ($p < 0.001$). Hence, relative differences without orientations in CBCT-based radiomic features showed high prognostic power for ESCC patients. In contrast, GF was not effective for predicting prognoses. In fact, GF did not have enough ability to predict prognoses of lung cancers, and few datapoints were related to unreliable gradients in [21]. In our study, appropriate gradients might not be obtained because only five datapoints were considered.

ARD was the most effective delta-radiomic feature for predicting prognoses, with ARD$_2$ being the best delta-radiomic feature set regarding the C-index, 0.821 (95% CI, 0.735–0.907). However, no significant differences in C-index were observed between ARD$_2$ and both ARD$_3$ and ARD$_4$. Therefore, ARDs at the early (2–3 weeks) to middle (4 weeks) stages of treatment had the same performance for predicting prognoses.

Shi et al. [22] used ARD but defined its mean from the first to arbitrary fractions as CBCT-based delta-radiomic features, finding a few delta-radiomic features with prognostic power for OS, which were calculated at the earliest tenth fraction of radiotherapy for lung cancer. Therefore, ARD-based delta-radiomic features at early treatment may provide high prognostic power for various types of cancers and analysis methods. ARD$_5$ in our study did not exhibit prognostic power, while the delta-radiomic features calculated after the tenth fraction in [22] showed prognostic power. This might be because delta-radiomic features at the tenth fraction were propagated into those at later fractions given the calculation of delta-radiomic features as the mean ARD in [22].

An et al. [36] demonstrated that delta-radiomic features from apparent diffusion maps of magnetic resonance imaging, which were prospectively acquired before and during treatment, would allow to predict the response to CCRT in ESCC patients. This was the first report of applying delta-radiomics to evaluate ESCC patients treated with CCRT. The RD-based delta-radiomic features from pretreatment to the tenth fraction of radiotherapy allowed to predict the treatment response and indicated that the response can be predicted by delta-radiomic features extracted at early stages of treatment [36]. As the treatment response can be related to prognosis, these results validate our finding that CBCT delta-radiomic features at early CCRT have high prognostic power.

Our results were consistent with those from previous studies, which analyzed thoracic cancers using delta-radiomics and determined that the variability of features derived from early treatment stages contributed to accurate prediction [22,36]. In addition, we found that the variability of CBCT-based radiomic features at middle treatment stages also promoted the prognostic power. Therefore, the variability of CBCT-based radiomic features at early to middle CCRT stages with respect to the first treatment day may be related to the treatment response and prognostic of
Fig. 4. Kaplan-Meier curves of OS and risk tables in high- and low-risk groups classified using delta-radiomic feature sets in LOOCV: (a) AD, (b) AAD, (c) RD, (d) ARD, and (e) GF. The red and blue lines indicate the high- and low-risk groups, respectively. Censorings are depicted as vertical lines on the curves. Ranges within parentheses in the HR and C-index denote the 95% CI. The risk tables denote the population of survival at days 0 (starting point), 1000, 2000, 3000, and 4000. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
ESCC, and the feature variability should be quantified by ARD. The relationship between the variability of radiomic features at approximately the first half of treatment and prognosis or treatment response should be interpreted by radio- oncology, chemo-oncology, or biology in future work.

Delta-radiomics is suitable for image-guided radiotherapy using CBCT images because the variability of radiomic features at multiple time points can be quantified by daily or weekly imaging. As in this study, the time point variabilities of radiomic features with high prognostic power for treatment can be evaluated and identified. Moreover, in clinical application, CBCT-based delta-radiomics may guide reconsideration of whether initial treatment strategies should be continued, stopped, or modified after specific time points. Because the prognoses of ESCC patients treated with CCRT could be predicted using delta- radiomic features over approximately the first half of treatments, treatment strategies might be reconsidered at least at early stages of treatment.

The quality of CBCT images is poorer than that of images acquired using other modalities. Consequently, a low CBCT image quality may distort the radiomic features. Transformations of the original CBCT images can be applied to mitigate noise and blurring. In radiomics, such transformations have been performed to extract radiomic features from images with enhanced properties. In this study, various transformations were applied to the original CBCT images, and radiomic features were extracted from the transformed images with reduced noise and blurring.

A repeatability or reproducibility test can be used to investigate the robustness of radiomic features in terms of CBCT image quality. In [37], several radiomic features showed robustness against poor CBCT image quality under the same conditions in a reliability test. Those approaches for handling CBCT image quality are post-image acquisition strategies. Future developments may involve pre-image acquisition strategies (e.g., novel iterative image reconstruction or artificial-intelligence-based image generation algorithms) for improving the CBCT image quality, aiming to further advance CBCT-based delta-radiomics.

This study was intended to be a feasibility study, and various limitations are related to its single-institution retrospective design. For instance, few participants were enrolled, and most samples were excluded because of data unavailability. Consequently, we could not evaluate the prediction models using an external dataset but only through LOOCV. Moreover, the prediction performance fluctuated given the wide ranges of the 95% CIs for the HRs and C-indices. We did not set exclusion criteria related to post-CCRT treatments to avoid further decreasing the number of enrolled patients. These limitations would be solved by designing a multicenter prospective study. A large trial should be performed in future work to verify the generality of our findings.

5. Conclusions

The prediction of prognoses of ESCC patients treated with CCRT based on the delta-radiomics using CBCT images from image-guided radiotherapy was evaluated in this study. We found that ARD-based delta-radiomic feature sets at approximately the first half of treatment allow to predict the prognoses of ESCC patients. Such features might enable to consider the significance of treatment or necessity of treatment replanning at early stages of CCRT in ESCC patients.

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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Appendix A. Supplementary data

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References


