Investigating Long-term Prognostication of CT-based Radiomics for Subgroup of High-risk Localized Prostate Cancer Patients Treated by Whole-pelvic Radiotherapy

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Research Article
Abstract

Background

To investigate capability of planning computed tomography (CT)-based radiomics for prediction of long-term prognostication, for the first time, in subgroup of high-risk localized prostate cancer (PCa) patients treated by whole-pelvic radiotherapy (WPRT).

Methods

A total of 64 high-risk localized PCa patients [training cohort (n=45) and validation cohort (n=19)] were enrolled. The planning CT and clinical data were collected. The least absolute shrinkage selection operator (LASSO) was used for model training in conjunction with 3-fold cross validation. The predictive performance of the model was assessed using the Area-under-the-curve (AUC) values generated from receiver operating characteristic analysis. The resultant radiomics signature was used for calculation of radiomics score (Rad-score) for every patients. A cut-off of the Rad-score was suggested for classification of the risk of having progression within 6 years, based on the evaluation of model accuracy, sensitivity, and specificity.

Results

The model incorporated 2 features: the run entropy of gray level run length matrix after Laplacian of Gaussian (LoG) filtering with a sigma value of 2 mm (RE-GLRLMo<sub>2mm</sub>); and the small area emphasis of gray level size zone matrix after LoG filtering with a sigma value of 4.5 mm (SAE-GLSZM<sub>4.5mm</sub>). AUC values of the training and testing cohorts were 0.76 and 0.71, respectively. With the cut-off as the third-quartile value for stratification into high-risk and low-risk group, the respective accuracy, sensitivity, and specificity of the radiomics signature were 77.8%, 83.3% and 55.6% in the training cohort and 84.2%, 86.7% and 75% in the testing cohort.

Conclusions

Radiomics signature based on pre-treatment planning CT images can be used as a potential biomarker for differentiating the risk of 6-year disease progression in high-risk localized PCa patients treated with WPRT. Further development is warranted that may help to support clinical decisions about follow-up and treatment options in this subgroup of patients.

Background

Prostate cancer (PCa) is a complex disease that consists of heterogeneous cohorts with different treatment options and variable prognosis (1). The treatment of low risk localized PCa is comparatively straight forward and could be performed by adopting radical prostatectomy, radiotherapy, or active surveillance (2). Unfortunately, high-risk localized PCa is more susceptible to recurrence, and therefore requires more complex multiple treatment modalities (3).
High-risk disease accounts for 15% of all localized PCa (4, 5). Presently, the Radiation Therapy Oncology Group (RTOG) and the National Comprehensive Cancer Network (NCCN) provides two of the recommendations for classifying patients’ risks (6, 7). However, classification of risk is not sufficient to indicate the most suitable treatment modalities for PCa patients due to intra-patient heterogeneity within the high-risk PCa group (3). It has been analyzed that the 5-year relapse-free survival was ranged from 49–80% (8), reflecting the need to further refine the subgroup stratification for indication of treatment of choice.

Numerous predictive tools have been developed for indication of treatment modalities of PCa patients (9). One of the most widely used approaches was suggested by Roach et al (10) to estimate the risk of lymph node metastasis. This method is often adopted to decide whether the high-risk localized PCa patients treated by external beam radiotherapy (EBRT) are indicated for prophylactic whole pelvic radiotherapy (WPRT), or otherwise prostate-only radiotherapy (PORT) should be adequate (11). Applying this formula, patients with estimated risk of lymph node involvement > 15% are suggested to include WPRT in their EBRT course. For the indicated patients, WPRT showed long-term benefits in progression-free survival against PORT (12, 13). Nevertheless, it is still not uncommon to observe high rate of treatment failure despite of use of WPRT. For instance, up to 40% of patients not able to achieve progression free survival for 4 years in a phase III randomized clinical trial (14). As such, a personalized stratification approach on the basis of individual risks of progression-free survival is pressingly needed for enhancing oncologic healthcare delivery for this PCa subgroup.

Precision medicine, a strategy to prescribe individualized management regimens according to sub-types (15), can be the way to improve the treatment for PCa patients. Recently, the technology of radiomics and machine learning has gained increasing popularity in clinical outcome prediction (16–18). Radiomics, first introduced by Lambin et al. (19), allows transformation of digital medical images into quantitative data. The data is hypothesized to contain genetic and molecular characteristics relevant to the oncological treatment. Recent studies have reported use of radiomics for prediction of treatment outcome in PCa patients receiving EBRT. Abdollahi et al. (20) reported the use of radiomics to the treatment response, GS and stage in prostate cancer. Gnep et al. (21) used textual feature of T2-weighted magnetic resonance imaging (MRI) to associate the biochemical recurrence after radiotherapy. In addition, computed tomography (CT) based radiomics can also be used for risk stratification (22). However, to our best knowledge, there is no research to include radiomics in predicting clinical outcome in the subgroup of high risk localized PCa patients receiving WPRT. The objective of our study was to develop prostate radiomic signature using planning CT images that are useful for prediction of 6-year progression free survival for the high-risk localized cohort of PCa patients who received WPRT. We attempted to investigate the potential of CT-based radiomics for long-term prognostication for this patient subgroup. Success of this study may provide valuable clinical insights into management of individual high-risk localized PCa patients according to their long-term prognosis, paving the way towards precision medicine for PCa patients.
Methods

Patient Source

Ethical approval was obtained for this retrospective study. The workflow of patient recruitment is illustrated in Fig. 1. 84 high-risk localized PCa patients treated between May 2009 and October 2014 were identified from a single center in this retrospective study. These patients were all estimated with the risk of pelvic lymph node involvement ≥ 15% by the Roach formula (10), and received EBRT as primary treatment with WPRT. After applying the exclusion criteria, 64 eligible patients were enrolled in this study. Enrolled patients were then randomized and assigned to the training cohort (n = 45) and testing cohort (n = 19). Patients’ age, disease-related data (pre-treatment TNM stage, GS and PSA level), treatment related data (radiotherapy technique and dose fractionation, and ADT drug regimen), follow-up duration, clinical outcome and Digital Imaging and Communications in Medicine (DICOM) data (planning CT images and structure set) were collected.

Treatment and follow-up regimen

All patients were treated by EBRT as the primary treatment. The clinical target volume (CTV) and planning target volume (PTV) used in the EBRT are detailed in Supplementary Material Table S1. The CTV for the prostate (CTV_{prostate}) was given 70–76 Gy in 2 Gy per fraction over 7–8 weeks with static field intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Simultaneously, the CTV for whole pelvic lymph nodes (CTV_{LN}) was given 44 or 50 Gy with 3-dimensional conformal radiotherapy (3DCRT) or VMAT. All plans were computed to meet the acceptance criteria and organ-at-risk (OAR) constraints (see Supplementary Material Table S2). Prior to EBRT, patients were given neoadjuvant androgen deprivation therapy (ADT). They first received 2 weeks of flutamide then 2 injections of 3-month luteinising hormone-releasing hormone agonist (LHRHa). After EBRT, patients were recommended to receive adjuvant LHRHa for up to 3 years. After completion of EBRT, patients had follow-ups at intervals of 3–6 months to monitor their disease. PSA levels were determined and evaluated at each visit. Imaging test would be provided if the PSA were found to be increased.

Clinical endpoint

The clinical endpoint of this study was the 6-year progression-free survival (PFS) of the patients after EBRT. It was defined as no biochemical recurrence, local recurrence, regional recurrence and/or distant metastasis within 6 years from the completion of the EBRT course. Deaths due to causes other than PCa were censored. Post-radiotherapy biochemical recurrence was defined according to the American Society for Therapeutic Radiology and Oncology consensus statement (23).

Image acquisition and segmentation

All patients were first instructed to empty their bladders, then to drink 400 cc of water an hour before the CT simulation to achieve comparable bladder status. During the CT scan, they were immobilized by
customized foam in supine position with both hands on the chest as in the treatment position. Non-contrast CT scans were performed using the CT simulator Philips Brilliance Big Bore with the following imaging parameters: slice thickness, 1.5 or 3 mm; tube voltage, 120 kVp; tube current, 350–450 mAs; field of view, 60 cm; matrix, 512 × 512; pixel spacing, 1.171875; and standard convolution kernel.

All structure sets collected including the CTV\textsubscript{prostate} were delineated manually on Eclipse version 13 (Varian, Palo Alto, California, USA) and clinically approved. The CTV\textsubscript{prostate} was contoured on planning CT slices by trained oncologists and was served as the volume of interest in this radiomics study. (Fig. 2)

**Image Pre-processing and Feature Extraction**

Image pre-processing and feature extraction of the planning CT images were conducted using a python-based software embedded with the PyRadiomics package (24). Isotropic resampling was applied to resize the images to 1 × 1 × 1 mm\(^3\) by linear interpolation to obtain a uniform volumetric spacing. Images were discretized to a fixed bin width of 10 Hounsfield units (HU) to attain a constant intensity resolution for the extraction of texture features. Also, images were reconstructed using the Laplacian of Gaussian (LoG) filter with sigma values of 0.5, 2, 3, 4, 4.5, 5 mm to extract features from various scales of edge detection and image smoothing. After image pre-processing, shape features (n = 14), first-order features (n = 126) and texture features (n = 511) of the CTV\textsubscript{prostate} were extracted as specified in Supplementary Material Figure S1 and Table S3. The shape features describe the 3-dimensional size and shape of the CTV\textsubscript{prostate}; the first-order features describe the voxel intensity distribution of the CTV\textsubscript{prostate}; while the texture features describe the voxel intensity relationship within the CTV prostate sub-regions. A total of 651 radiomic features were extracted from each patient’s planning CT set.

**Feature Selection and Modelling**

The extracted features were processed as illustrated in Fig. 3. Before feature selection took place, features from the training cohort were centered and scaled to avoid individual features from being over/under-presented. Features from the testing cohort were then normalized based on the mean and standard deviation of the centered and scaled training data.

Then, feature selection was performed by using statistical approaches consecutively to select a smaller set of features from the training data into our model. First, the Mann-Whitney U test was performed to assess clinical association of each radiomic feature. Features with p > 0.05, which showed no statistical difference across the outcome groups, were removed. Second, Spearman's rank correlation coefficient was calculated to evaluate the pair-wise correlation of the features to identify redundant features. If two features had an absolute correlation coefficient ≥ 0.4, the one with the largest mean absolute correlation was removed.

The remaining features were then included in the modelling procedure. Modelling was done by logistic regression in conjunction with Least Absolute Shrinkage and Selection Operator (LASSO) penalty and 3-fold cross-validation. LASSO penalty was applied to minimize prediction errors and to simplify the model.
It would help to select the most predictive features by penalizing the sum of the absolute values of feature coefficients. Features with minor contribution to the model would be forced to reduce the coefficient to become zero, and thus the feature would eventually be removed from the model. For the 3-fold cross-validation, the training data was randomly divided into three sub-sets. 2 out of 3 sub-sets were used for training while the remaining one was used for validation. The training-validating process was repeated three times with each sub-set served as the validation data once. Apart from testing the model and minimizing bias, 3-fold cross-validation was also used to find the optimal regularization parameter for LASSO, known as lambda. The model with the lambda that gave the greatest area under receiver operating characteristic (ROC) curve (AUC) was eventually selected. This model training process was repeated 1000 times, resulting in 1000 models.

All the above features processing were performed using the R software (version 3.6.3). The following R packages were used: 1) the “base” package for randomization and normalization; 2) the “stats” package for calculating Mann-Whitney U test P-values and Spearman’s rank correlation coefficients; 3) the “caret” package for analysing pair-wise correlations; 4) the “glmnet” package for performing logistic regression with cross-validation and LASSO penalty; and 5) the “ROCR” and “cvAUC” packages for ROC analysis and AUC calculation.

**Development of Radiomics Signature**

Among the formulated models, those with good AUC were used to develop the radiomics signature. Each feature coefficient ($\beta$) and the intercept in the radiomics signature were calculated by averaging those values of the included models. Radiomics signature is illustrated by the following equation:

$$\text{Rad-score} = \sum_{i=1}^{n} \beta_i \times \text{feature}_i + \text{intercept} \quad \text{(Eq. 1)}$$

The radiomics score (Rad-score) of each patient was calculated by the sum of weighted features and intercept by the equation.

A cut-off of the Rad-score was suggested based on the evaluation of model accuracy, sensitivity, and specificity. The cut-off can be used to classify whether the patient is more likely to have 6-year PFS based on their Rad-score. The predictive performance of each derived model in the training and testing cohorts was assessed using the AUC values generated from ROC analysis of the predicted probabilities. The average AUC values of the models were calculated. The performance of the derived radiomics signature was evaluated in terms of accuracy, sensitivity, and specificity.

**Results**

Clinicopathological characteristics of the training and testing cohort are listed in Table 1. There was no significant difference between the training and testing cohorts in the distribution of the listed characteristics. For the clinical endpoint, the median PFS of all recruited patients was 81.5 months. Patients with 6-year PFS constituted 80% and 78.9% of the training and testing cohorts respectively. Thirteen patients (20.3%) who experienced recurrence and/or metastasis within 6 years after the
completion of the EBRT course were included, representing 20% and 21.1% of the two corresponding cohorts.
Table 1
Clinicopathological characteristics of the study population.

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<th>Testing cohort</th>
<th>P-value</th>
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<td>≥8</td>
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<td>32.8</td>
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<td>CTV _{prostate} volume (mm(^3))</td>
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<td>39951.5</td>
<td>41695</td>
<td>38943</td>
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* Mann-Whitney U test; † Likelihood ratio chi-square test; ‡ Fisher’s exact test
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<th>Testing cohort</th>
<th>P-value</th>
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<td>CTV\textsubscript{LN} dose (Gy)</td>
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<tr>
<td>44</td>
<td>11 (17.2%)</td>
<td>7 (15.6%)</td>
<td>4 (21.1%)</td>
<td>0.719‡</td>
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<tr>
<td>50</td>
<td>53 (82.8%)</td>
<td>38 (84.4%)</td>
<td>15 (78.9%)</td>
<td></td>
</tr>
<tr>
<td>CTV\textsubscript{prostate} dose (Gy)</td>
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<tr>
<td>&lt; 76</td>
<td>12 (18.8%)</td>
<td>8 (17.8%)</td>
<td>4 (21.1%)</td>
<td>0.739‡</td>
</tr>
<tr>
<td>≥ 76</td>
<td>52 (81.3%)</td>
<td>37 (82.2%)</td>
<td>15 (78.9%)</td>
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<td>PTV\textsubscript{LN} treated with</td>
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<tr>
<td>3DCRT</td>
<td>10 (15.6%)</td>
<td>6 (13.3%)</td>
<td>4 (21.1%)</td>
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<td>39 (86.7%)</td>
<td>15 (78.9%)</td>
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<td>PTV\textsubscript{prostate} treated with</td>
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<tr>
<td>IMRT</td>
<td>9 (14.1%)</td>
<td>5 (11.1%)</td>
<td>4 (21.1%)</td>
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<tr>
<td>VMAT</td>
<td>55 (85.9%)</td>
<td>40 (88.9%)</td>
<td>15 (78.9%)</td>
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<td>62 (96.9%)</td>
<td>44 (97.8%)</td>
<td>18 (94.7%)</td>
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<td>52 (81.3%)</td>
<td>36 (80%)</td>
<td>16 (84.2%)</td>
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<tr>
<td>Follow-up (months)</td>
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<tr>
<td>Median</td>
<td>88</td>
<td>91</td>
<td>88</td>
<td>0.872*</td>
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<td>PFS (months)</td>
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<td>Median</td>
<td>81.5</td>
<td>81</td>
<td>85</td>
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<tr>
<td></td>
<td>13 (20.3%)</td>
<td>9 (20%)</td>
<td>4 (21.1%)</td>
<td>1.00‡</td>
</tr>
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<tr>
<td>Regional failure</td>
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<td>0</td>
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*Mann-Whitney U test; †Likelihood ratio chi-square test; ‡Fisher's exact test
Among the 1000 trained models, 799 models with two selected features were used to create the radiomics signature. The two selected features were both textural, they were Feature 1: the run entropy of gray level run length matrix after LoG filtering with a sigma value of 2 mm (RE-GLRLM$\sigma_{2mm}$); and Feature 2: the small area emphasis of gray level size zone matrix after LoG filtering with a sigma value of 4.5 mm (SAE-GLSZM$\sigma_{4.5mm}$). RE-GLRLM$\sigma_{2mm}$ and SAE-GLSZM$\sigma_{4.5mm}$ showed a significant difference of the feature values between patients with or without 6-year PFS with P-values of 0.0208 and 0.0191. The radiomics signature was represented using the following equation:

$$\text{Rad-score} = 0.291 \text{ (RE-GLRLM}_{\sigma_{2mm}}) + 0.358 \text{ (SAE-GLSZM}_{\sigma_{4.5mm})} - 1.47 \text{ (Eq. 2)}$$

Averaged AUC values of the training and testing cohorts were 0.756 (95% confidence interval: 0.756–0.757) and 0.707 (95% confidence interval: 0.706–0.707) (Fig. 4). With the cut-off as the third-quartile value (i.e., -1.11), patients were stratified into high-risk group (Rad-score $\geq$ -1.11) and low-risk group (Rad-score < -1.11). The respective accuracy, sensitivity and specificity of the radiomics signature were 77.8%, 83.3% and 55.6% in the training cohort and 84.2%, 86.7% and 75% in the testing cohort.

**Discussion**

In the present study, we selected the key radiomic features among the large arrays of data extracted from CTV$_{prostate}$ in the pretreatment planning CT images and developed a two-feature radiomics signature that predicts the 6-year PFS in high-risk localized PCa patients who received EBRT as primary treatment with WPRT. Our models achieved high consistent predictive performance, as evinced in the average AUC of 0.76 and 0.71 in the training and testing cohorts respectively. Because planning CT used for EBRT is largely standardized and calibrated for dose calculation, the use of planning CT in radiomics can utilize its standard for the benefit of better reproducibility and robustness of the radiomics features (22). For application, patients with a rad-score lower than -1.11 were more likely to experience 6-year PFS with satisfactory accuracy, sensitivity, and specificity in both the training and testing cohorts. Predicting treatment outcome prior to treatment commencement would assist clinical decision making and patient management after primary treatment. With growing evidence that radiomics is powerful in risk stratification, it paves the potentials of personalized precision medicine.

The developed radiomics signature consisted of two texture features, namely the GLRLM Run Entropy (RE-GLRLM$\sigma_{2mm}$) and SAE-GLSZM Small Area Emphasis (GLSZM$\sigma_{4.5mm}$). RE-GLRLM$\sigma_{2mm}$ quantifies the heterogeneous texture pattern within the CTV$_{prostate}$ by representing the variations in allocation of run lengths and gray levels. SAE-GLSZM$\sigma_{4.5mm}$ measures the quantities of smaller-sized zones and fine
textures within the CTV\textsubscript{prostate} by representing the distribution of consecutive voxels that share identical intensity values. As these two features bear positive weightings in our radiomic signature, with higher values of RE-GLRL\textsubscript{σ2mm} and SAE-GLSZM\textsubscript{σ4.5mm}, the rad-score becomes higher and indicates that the CTV\textsubscript{prostate} of that patient exhibits a more heterogeneous 3-dimensional pattern. Simultaneously, a higher rad-score in our study implies a higher possibility of experiencing disease progression within 6 years after treatment. It is an advantage of using radiomics analysis which could effectively extract distinctive characteristics of the malignant mass and quantify respective heterogeneity, which is profoundly related to prognosis and therapeutic response for oncological diseases (25). Similar investigation has been done on other malignancies. These include breast cancer, which showed that a variety of texture features are correlated with angiogenesis and hypoxia, indicating the aggressiveness of the malignancy (26, 27); and nasopharyngeal carcinoma, which showed the capability of radiomics in predicting distant metastasis (28). Besides, previous study also suggested that more heterogenous PCa tumor exhibits greater resistance to therapies (29). This may explain why a higher rad-score is more predictive of disease progression in our study.

Biochemical failure or clinical failure after primary EBRT is not uncommon for PCa patients. It has been reported that biochemical failure would affect up to 40% of patients in 10 years after EBRT (30). About 25% of patients with biochemical failure would develop into clinical failure in 8 years with symptoms due to the recurrent disease (31). Many of the these patients would eventually be managed by palliative approaches by either observation or ADT (32). However, selected patients with biochemical failure or isolated local recurrence without coexisting metastatic lesions could be benefited from curative intent salvage treatments including salvage prostatectomy, brachytherapy, and stereotactic body radiotherapy (SBRT), etc (33). Using our model with pretreatment identification of patients who are more likely to have disease progression after treatment, patients could be promptly followed up by the state-of-the-art imaging examination (34), thus increasing the chance of getting identified when salvage treatment would be feasible.

Prediction of failure has been of interest of researchers. Many prediction nomograms have been developed over the past decades, such as those for prediction of patients’ survival after radical prostatectomy failure (35), and metastatic patients (36, 37). In particular, a nomogram for prediction of 10-year biochemical recurrent-free survival in patients treated by EBRT was developed by Zelefsky et al. (38) The nomogram depended on pre-treatment PSA, GS, staging and treatment parameters such as radiation dose and use of ADT. It resulted in an accuracy of 72%, which can be compared to our radiomics model which achieved an accuracy of 77.8%. Radiomics can consider the texture, which is not able to be determined by traditional criteria. Texture might be a better biomarker for prediction purpose because prostate cancer is associated with significant intratumoral heterogeneity as discussed in the previous paragraph. Moreover, the selection of texture features in our model is in line with previous literature using MRI radiomics on predicting distant metastasis in locally advanced non-small cell lung cancer (39), and biochemical recurrence following EBRT in PCa (21). In addition, the usefulness of CT-
based radiomics studies was indicated in perfusion-CT (40) and non-contrast CT (22) that texture features were useful for risk stratification in PCa.

Various limitations exist in our study. Firstly, it is a retrospective study with a limited number of samples (n = 64) recruited from a single center. Also, validation was done by randomly assigning a portion of the samples to create a testing cohort, which may not be able to ensure generalizability of the model. Thirdly, despite delineation protocol (41) is adopted, the segmentation of the volume of interest for radiomics features extraction was done manually by Oncologists. Semi-automatic tumor segmentation with computer assistance might be more suitable for segmentation in radiomics studies for yielding more reproducible features. However, this study was the first of its kind to utilize radiomics analysis methods on pretreatment planning CT of high risk localized PCa patient for long-term survival prediction, which is a major novelty of this study. Our study suggested the possibility of using radiomics signature as a potential biomarker for high-risk localized PCa patients using CT images, which are readily available for every PCa patients treated by EBRT. In future, MRI-based larger cohort multi-center study is warranted for bench-to-bedside model translation. In addition, this method could be further developed for assisting other clinical decision-making for this disease. One potential area of interest is to assist in choosing between WPRT versus PORT (42). In the present study, all patients underwent EBRT with WPRT. Although WPRT is believed to improve disease free survival, the increase of toxicity due to extensive irradiation volume to the gastro-intestinal tract is of concern (42). Moreover, due to the conflicting results of the two large-scale clinical trials by the RTOG 9413 group (14) and the French Genitourinary Study Group (GETUG)-01 group (43), hospitals may routinely offer PORT instead of WPRT for the same cohort of patients (44). It will be our next phase of the study to develop radiomics models for high-risk localized PCa patients treated with PORT. Therefore, a decision support system in choosing WPRT or PORT could be introduced by generating pretreatment prediction of disease progression with the two regiment respectively.

Conclusions

Radiomics signature based on pre-treatment planning CT images could be used as a potential biomarker for differentiating the risk of 6-year disease progression post PCa radiotherapy. The results of this study showed that the quantitative method of radiomics signature can provide information for follow-up support for the clinical complexity of high-risk localized PCa. Further development based on this method may help to plan for precision radiotherapy for PCa patients, which may include selection of patients for WPRT versus PORT.

Abbreviations

CT: Computed tomography; PCa: Prostate cancer; WPRT: Whole-pelvic radiotherapy; LASSO: Least absolute shrinkage selection operator; AUC: Area-under-the-curve; Rad-score: Radiomics score; LoG: Laplacian of Gaussian; RE-GLRLMσ2mm:
The run entropy of gray level run length matrix after LoG filtering with a sigma value of 2 mm; SAE-GLSZMσ4.5mm: The small area emphasis of gray level size zone matrix after LoG filtering with a sigma value of 4.5 mm; RTOG: Radiation Therapy Oncology Group; NCCN: National Comprehensive Cancer Network; EBRT: External beam radiotherapy; PORT: Prostate-only radiotherapy; MRI: Magnetic resonance imaging; DICOM: Digital imaging and communications in medicine; CTV: Clinical target volume; PTV: Planning target volume; CTV for the prostate: CTVprostate; IMRT: Intensity-modulated radiotherapy; VMAT: Volumetric modulated arc therapy; CTV for the whole pelvic lymph nodes: CTVLN; 3-dimensional conformal radiotherapy: 3DCRT; Organ-at-risk: OAR; ADT: Androgen deprivation therapy; LHRHa: Luteinising hormone-releasing hormone agonist

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of the Hong Kong Polytechnic University and the New Territories East Cluster Clinical & Research Ethics Committee. We confirm that all methods were carried out in accordance with relevant guidelines and regulations. Informed consent was waived by the institutional review board of the Hong Kong Polytechnic University and the New Territories East Cluster Clinical & Research Ethics Committee because of the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

WSL: Conceptualization, Methodology, Writing; SKL: Methodology, Data curation; PTW, KYN: Writing, Methodology, Preparation of tables; CHT, TCL, KCC, YKC: Preparation of figures and tables; VCWT, SWYL, MYL: Methodology; QJW, JC: Conceptualization. All authors read and approved the final manuscript.
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References


Figures
Clinically localized PCa patients
1. Roach score ≥ 15%
2. Received WPRT
3. Follow-up duration ≥ 6 years (n=84)

Exclusion criteria:
1. Second malignancies other than PCa (n=11)
2. Previously treated for PCa (n=2)
3. Unknown or absent of pre-treatment biopsy result (n=5)
4. Death due to causes other than PCa (n=2)

Data collection
1. Clinical and treatment data
2. Planning CT images
3. Radiotherapy structures set (n=64)

Training cohort (n=45) Testing cohort (n=19)

**Figure 1**
A diagram showing the workflow of patient recruitment

![Figure 1](image1)

**Figure 2**
Axial planning CT images with manually-delineated CTVprostate contours (blue overlay). (a) The CTVprostate included the entire prostate gland. (b) The CTVprostate included the entire prostate gland with proximal two-thirds of seminal vesicles

![Figure 2](image2)
Figure 3

A workflow of data processing, feature selection, modelling, development of radiomics signature, and performance evaluation
Figure 4

A graph showing the averaged ROC curves developed model applied in the training and testing cohorts

Supplementary Files

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- 6.Supplementarymaterial.docx