Statistical Analysis of Survival Models Using Feature Quantification on Prostate Cancer Histopathological Images

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Received: 06 November 2018   Accepted: 14 June 2019   Published: 27 September 2019

Abstract

Background: Grading of prostatic adenocarcinoma is based on the Gleason scoring system and the more recently established prognostic grade groups. Typically, prostate cancer grading is performed by pathologists based on the morphology of the tumor on hematoxylin and eosin (H and E) slides. In this study, we investigated the histopathological image features with various survival models and attempted to study their correlations. Methods: Three texture methods (speeded-up robust features, histogram of oriented gradient, and local binary pattern) and two convolutional neural network (CNN)-based methods were applied to quantify histopathological image features. Five survival models were assessed on those image features in the context with other prostate clinical prognostic factors, including primary and secondary Gleason patterns, prostate-specific antigen levels, age, and clinical tumor stages. Results: Based on statistical comparisons among different image features with survival models, image features from CNN-based method with a recurrent neural network called CNN-long-short-term memory provided the highest hazard ratio of prostate cancer recurrence under Cox regression with an elastic net penalty. Conclusions: This approach outperformed the other image quantification methods listed above. Using this approach, patient outcomes were highly correlated with the histopathological image features of the tissue samples. In future studies, we plan to investigate the potential use of this approach for predicting recurrence in a wider range of cancer types.

Keywords: Histopathological image, image features, neural networks, prostate cancer, survival models

INTRODUCTION

Survival analysis is a means for predicting patient outcomes by providing invaluable information for selecting treatment. Predicting prostate cancer survival outcomes is a significant challenge. Following radical prostatectomy, men must be closely monitored for the evidence of recurrence. This is typically done via prostate-specific antigen (PSA) blood tests. A detectable or rising PSA after surgery is the evidence of biochemical recurrence. The measure of time from surgery to biochemical recurrence is biochemical recurrence-free survival (bRFS). Multiple studies examined predictors of bRFS using quantitative histopathological features with some survival models. However, numerous prediction tools utilized whole-slide images (WSIs) to assess prostate cancer recurrence and predicted the likely outcomes resulting from treatments. Few of these studies simultaneously considered clinical factors (primary and secondary Gleason patterns, PSA value, age, tumor stage) and tissue WSIs to correlate with recurrence under different survival models.

The Gleason scoring system for prostate cancer remains one of the best predictors for prostate cancer progression and recurrence, despite significant interobserver reproducibility among pathologists. A more recently adapted grading system stratifies patients into five prognostic grade groups based on their Gleason patterns: grade Group 1 (Gleason ≤ 3 + 3 = 6), grade Group 2 (Gleason 4 + 3 = 7), grade Group 3 (Gleason 3 + 4 = 7), grade Group 4 (Gleason 4 + 4 = 8), and grade Group 5 (Gleason 5 + 5 = 10). In this study, we investigated the histopathological image features with various survival models and attempted to study their correlations.

Methods: Three texture methods (speeded-up robust features, histogram of oriented gradient, and local binary pattern) and two convolutional neural network (CNN)-based methods were applied to quantify histopathological image features. Five survival models were assessed on those image features in the context with other prostate clinical prognostic factors, including primary and secondary Gleason patterns, prostate-specific antigen levels, age, and clinical tumor stages. Results: Based on statistical comparisons among different image features with survival models, image features from CNN-based method with a recurrent neural network called CNN-long-short-term memory provided the highest hazard ratio of prostate cancer recurrence under Cox regression with an elastic net penalty. Conclusions: This approach outperformed the other image quantification methods listed above. Using this approach, patient outcomes were highly correlated with the histopathological image features of the tissue samples. In future studies, we plan to investigate the potential use of this approach for predicting recurrence in a wider range of cancer types.

Keywords: Histopathological image, image features, neural networks, prostate cancer, survival models

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Website: www.jpathinformatics.org

DOI: 10.4103/jpi.jpi_85_18

How to cite this article: Ren J, Singer EA, Sadimin E, Foran DJ, Qi X. Statistical analysis of survival models using feature quantification on prostate cancer histopathological images. J Pathol Inform 2019;10:10-30. Available FREE in open access from: http://www.jpathinformatics.org/text.asp?2019/10/1/30/268079

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Grade Group 2 (Gleason 3 + 4 = 7), Grade Group 3 (Gleason 4 + 3 = 7), Grade Group 4 (Gleason 4 + 4 = 8, 3 + 5 = 8, and 5 + 3 = 8), and Grade Group 5 (Gleason 4 + 5 = 9, 5 + 4 = 9, and 5 + 5 = 10). Figure 1 shows an example of Giga-pixel WSI with different Gleason patterns. The green-framed patch contains Gleason pattern 3; the blue-framed patch contains Gleason pattern 4; and the red-framed patch contains Gleason pattern 5. In this study, we conducted experiments on public prostate cancer dataset using different feature quantification methods and recurrence analysis using different survival models. Histopathological image features were quantified through texture methods and neural network-based approaches. We focused on the prostate cancer grade groups of 1–4. The bRFS was applied as the time to recurrence for prostate cancer progression analysis.

**Materials and Methods**

**Materials**

In this study, we used the prostate dataset from the Genomic Data Commons (GDC).[20] The dataset included whole-slide histopathological images from patients and their corresponding clinical reports, including the primary and secondary Gleason pattern, patients’ PSA value, age, and tumor stage. All the image data, annotations of Gleason score, and clinical information were publicly available.

We selected the patients with low-risk (Gleason score 3 + 3), intermediate-risk (Gleason score 3 + 4 or 4 + 3), and high-risk prostate cancer (Gleason score 4 + 4) because those patient populations show a reasonable range of prognoses for our analysis. We excluded patients with Gleason Grade Group 5 patients in this study due to poor prognosis of their disease.[21] Considering the high computational cost on the Giga-pixel tissue WSIs, existing WSIs classification and recurrence analysis approaches were focused on effectively utilizing the cropped patches from region of interests.[22‑27] For image preparation, we adopted the two-step cropping-selecting process. First, original patches were automatically generated within each WSI under ×40 with a patch size of 4096 × 4096. Second, the patches with the tissue accounting for at least 20% of the whole area were selected for our experiments. The number of WSIs and cropped patches under different Gleason scores is shown in Table 1.

**Methods**

Initially, we utilized various quantification methods to extract image features from WSIs. Next, the recurrence analysis was performed on the combination of image features and clinical factors utilizing different survival models, as shown in Figure 2. Hazard ratios using different survival models were calculated to indicate the correlation between image features (or in context of clinical factors) and recurrence; the higher the hazard ratio, the higher the correlations.

**Image feature quantification**

We adopted five approaches for the purpose of feature quantification including unsupervised and supervised methods. The unsupervised texture methods consisted of speeded-up robust features (SURFs),[28] histogram of oriented gradients (HOGs),[29] and local binary pattern (LBP).[30] The two supervised methods are based on convolutional neural networks (CNNs). For supervised methods, we randomly selected 20% of the cases as testing set, 10% as validation set, and the remaining as training set.

**Texture features**

We chose three texture methods for prostate cancer histopathological image analysis. They were rotation, translation, and scale- and intensity-invariant which were suitable for descriptions of the texture features within WSIs.

The SURF[28] is partly inspired by the scale-invariant feature transform (SIFT) descriptors. The standard version of SURF is several times faster than SIFT and more robust against different image transformations than SIFT. The image is transformed into coordinates, using the multiresolution pyramid technique, to copy the original image with a pyramidal Gaussian or Laplacian pyramid shape to obtain an image with the same size but with reduced bandwidth. The HOG[29] counts occurrences of gradient orientation in a local region of an image. It is similar to that of edge-orientation histograms, SIFT descriptors, and shape contexts but differs in that it is computed on a dense grid of uniformly spaced cells and uses overlapping local contrast normalization for improved accuracy. The LBP[30] is used to

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**Table 1: The number of whole-slide images and their corresponding automatically selected patches under different Gleason scores composing from a sum of Gleason patterns 3+3, 3+4, 4+3, and 4+4 prostate prognostic grading groups**

| Gleason score | 3+3 | 3+4 | 4+3 | 4+4 |
|---------------|-----|-----|-----|-----|
| # WSIs        |    |     |     |     |
| # patches     | 43 | 144 | 99  | 49  |
| # patches     | 1229 | 4753 | 2997 | 1597 |

WSIs: Whole-slide images
model the image local features in texture spectrum units in a multiresolution gray-scale mode. It is based on recognizing local binary unit patterns for any quantization of the angular space and spatial resolution.

The image features for each patch were generated using a bag-of-words approach\cite{31} from the texture features of different texture methods. By treating image features as words, a bag of words is a sparse vector of occurrence counts (histogram) of a vocabulary of local image features. In the bag-of-word approach, it converts vector-represented texture features to codewords, which also produce a codebook. The image features are mapped to certain codewords through the clustering process, and the image is then represented by the histogram of the codewords. Empirically, we use 100 as the number of cluster centers to report the best performance for texture features.

To select the texture features for WSIs, we apply principal component analysis (PCA)\cite{32} of the image features for all patches within a WSI due to correlations among the patches.

**Convolutional neural network-based features**

In recent years, with the advances of deep learning, studies using CNNs have demonstrated significant improvement on histopathological image classification\cite{27,33,34,35,36} and segmentation.\cite{33,34,37,38} For the WSIs, applications based on CNNs have been widely developed.\cite{39,40,41} In our study, we adopted two approaches to obtain CNN-based features. The first one was using the neural network to obtain image features for each patch, and then the features for WSIs were obtained by utilizing PCA on all patches. The CNN employed in the study is shown in Table 2. The input to the network was the cropped patches from prostate pathological WSIs. The activations from the second to the last layer were considered as the image features of the input samples. To train the network with patches, we assigned Gleason pattern as the ground truth annotation for the patch. The GDC WSIs have been previously graded with the primary and secondary patterns, as well as the final Gleason score given.

![Figure 2: Outline of image feature quantification from whole-slide images and assessed by various survival models](image)

**Table 2: The convolutional neural network applied in our approach**

| Layer | Filter size, stride | Output W × H × N |
|-------|---------------------|-------------------|
| Input | -                   | 256×256×3         |
| Conv  | 11×11, 4            | 55×55×96          |
| Max-pooling | 3×3, 2 | 27×27×96          |
| Conv  | 5×5, 1              | 27×27×256         |
| Max-pooling | 3×3, 2 | 13×13×256        |
| Conv  | 3×3, 1              | 13×13×384         |
| Conv  | 3×3, 1              | 13×13×384         |
| Conv  | 3×3, 1              | 13×13×256         |
| Max-pooling | 3×3, 2 | 6×6 × 256    |
| FC6   | -                   | 4096              |
| FC7   | -                   | 4096              |
| FC8, FC9 | -         | 2, 4              |

All the Conv are followed by ReLU. For the FC, the FC6 and FC7 are followed by the ReLU and dropout layer with the dropout ratio as 0.5; FC8 and FC9 are both at the top of FC7. Conv: Convolution layers, ReLU: Rectified linear units, FC: Fully connected layers, W×H×N: Height×Width×Channel

To model variations among Gleason patterns within a WSI, we used the multitask architecture to enable the network to learn as much information about the Gleason patterns from the patches of a WSI as possible. During the training process, we assigned the primary pattern and the sum of primary pattern and secondary pattern (Gleason score) as labels for each patch and use the following multitask loss function:

\[
L_{\text{multitask}} = -\sum_{i=0}^{N} t_i^p \log(\hat{t}_i^p) - \sum_{i=0}^{N} t_i^s \log(\hat{t}_i^s) \tag{1}
\]

where for the \(i^{th}\) image within the batch of \(N\) images, \(t_i^p\) and \(t_i^s\) encoded the Gleason grading for the primary pattern and the sum score and \(\hat{t}_i^p\) and \(\hat{t}_i^s\) encoded the predicted grading of the model. The one-hot encoding is a process by which categorical variables are converted into a form that could be provided to CNN to do a better job in classification. The results suggested...
that using the primary Gleason pattern and the Gleason score together achieved the best estimate of risk of recurrence by capturing local and global image feature distribution more efficiently than using either one alone.

For the second approach, we treated the cropped patches from the WSI as an image sequence and used one type of recurrent neural network (RNN) called long-short-term memory (LSTM) to explore the long-term dynamic information of the patch spatial sequence within the WSI. We denoted the method as CNN features with LSTM (CNN + LSTM). The LSTM could fully leverage the patch spatial sequence within a WSI to get the representative features that model the global Gleason score of the WSI and the distribution of the Gleason patterns among the WSI. Recently, the LSTM model has been successfully used in speech recognition,[42,43] language translation models,[44] image captioning,[45] and video classification.[46] Compared with the traditional RNNs, LSTM is more effectively in long-range and short-term spatial sequence modeling. In general, given an input feature sequence \((x_1, x_2, ..., x_T)\), the LSTM outputs the output sequence \((y_1, y_2, ..., y_T)\). The hidden layer of LSTM is computed recursively from \(t = 1\) to \(t = T\) with the following equations:

\[
i_t = \sigma(W_ix_t + W_hh_{t-1} + W_oc_{t-1} + b_i)
\]

\[
f_t = \sigma(W_if_i + W_hf_{t-1} + W_oc_{t-1} + b_f)
\]

\[
c_t = f_t\cdot c_{t-1} + i_t\cdot\tanh(W_xi_t + W_hh_{t-1} + b_c)
\]

\[
o_t = \sigma(W_io_i + W_ho_{t-1} + W_oc_{t-1} + b_o)
\]

\[
h_t = o_t\cdot\tanh(c_t)
\]

where \(x_i\) is the network activations of the \(i^\text{th}\) patch, \(h_i\) is the hidden vector, \(i, c, f, o\) are, respectively, the activation vectors of the input gate, memory cell, forget gate, and output gate. \(W\) terms denoted the weight matrices connecting different units, \(b\) terms denoted the bias vectors, and \(\sigma\) is the logistic sigmoid function. From the above equations, we can see the memory cell \(c_t\) in LSTM having two inputs: the weighted sum of the current inputs and the previous memory cell units \(c_{t-1}\), which enables the model to learn when to forget the old information and when to consider new information. The output gate \(o_t\) controls the propagation of information to the following step.

Since we utilized the spatial characteristic encoded features from CNN, the training process of LSTM of patches within WSIs was formed in a spatial format instead of time sequential manner. As shown in Figure 3, we used the image coordinates to indicate the location of each patch in the patch spatial sequence. In this way, we considered both the unique characteristics of each patch and the fine-grained variations between patches. For one prostate WSI, the patches were fed into the network to get the activations from the second to the last layer. Then, we utilized a one-layer LSTM to recursively map the activations of each patch to a feature vector. In addition, the average pooling layer was applied on top of the network to get a feature vector as the computational image features for the WSI. The number of hidden units for each LSTM is 1024. During the training process, we applied the multitask loss and assign the primary pattern and the Gleason score for the WSIs.

Survival models

To evaluate the performance of various survival models using different image features quantified by textural and CNN-based methods on patients with prostate cancer, we used the bRFS since their initial treatment as a time-to-recurrence variable for survival models. Using survival models, we assessed the image features related to recurrence hazard risk scores in the context of other clinical prognostic factors, including the primary and the secondary Gleason patterns, PSA, age, and clinical tumor stage.

The hazard risk scores of image features in the context of clinical mean a measure of prostate cancer recurrence risk ratio, commonly in time-to-event analysis or survival analysis. The survival models evaluated in our study include multivariate Cox proportional-hazards model,[47] Cox regression by an elastic net penalty (COX-EN),[48] parametric proportional-hazard model (PH-EX),[49] parametric proportional-hazard model with log-normal distance (PH-LogN),[49] and parametric proportional-hazard model with log-logistic distance (PH-LogL).[49]

For the high-dimensional data, univariate Cox regression was applied to the computational image features. Only those with Wald test, \(P < 0.05\) is selected in conjunction with clinical factors as inputs of the survival models. The Cox proportional-hazards model is a popular regression model for the analysis of survival data. It is a semi-parametric method for adjusting survival rate estimates to quantify the effect of predictor variables. In contrast with parametric models, it makes no assumptions about the shape of the so-called baseline hazard function. It represents the effects of explanatory variables as a multiplier of a common baseline hazard function \(H_0\). Given the patients \((t_i, l_i, x_i)\), where \(i = 1, 2, ..., N\), we have the \(t_i\) as the patient’s recurrence time for individual \(i\); \(l_i\) is the label of the censored data that equals 1 if the recurrence occurred at that time and 0 if the patient has been censored; and \(X_i\) as the vector of covariates of the selected image features and clinical factors.

The hazard function is the nonparametric part of the Cox proportional-hazards regression function corresponding to

\[
H(X_i, l_i, t_i) = H_0(t) \exp \sum_{j=1}^{p} x_{ij} \beta_j
\]

Here, \(x_{ij}\) is the image features \(j\) for patient \(i\), where \(j = 1, 2, \ldots p\) and \(\beta_j\) is the Cox regression parameter for each patient.

The hazard ratio is derived from \(H(X_i, l_i, t) = \frac{H(X_i, 1, t)}{H_0}\). 

\[
H(X_i, l_i, t) = H_0(t) \exp \sum_{j=1}^{p} x_{ij} \beta_j
\]
representing the relative risk of instant failure for patients having the predictive value $X_i$ compared to the ones having the baseline values. Here, $d_i$ is weighting parameters for each patient.

$$HR(X_i) = \sum_{j} d_i (X_i \beta_j - \log(\sum_{j} e^{X_i \beta_j}))$$

(8)

For the COX-EN, the elastic net penalty $\hat{\beta}$ is given in the equation below. It is a mixture of the L1 (Lasso) and L2 (ridge regression) penalty. Here, $\alpha$ is the ratio between L1 and L2 for elastic net.

$$\hat{\beta} = \arg\max_{\beta} \left[ \frac{2}{n} \left( \sum_{i=1}^{N} X_i^T \beta_i - \log \left( \sum_{i=1}^{N} e^{X_i^T \beta_i} \right) \right) - \lambda P_{\alpha}^\beta \right]$$

(9)

where $P_{\alpha}^\beta = \lambda \left[ \alpha \left( \sum_{i=1}^{p} |\beta_i| \right) + \frac{1}{2} (1 - \alpha) \sum_{i=1}^{p} \beta_i^2 \right]$,

(10)

Based on the assumption that the effect of the covariates is to increase or decrease the hazard by a proportionate amount at all durations, the parametric proportional-hazard model is a location-scale model for arbitrary transform of the time variable $t_i$, leading to accelerated failure time model with different penalty distance functions. The distance functions we use for parametric proportional-hazard models are exponential transformation (PH-EX), log-normal (PH-LogN), and log-logistic (PH-LogL) distances.

The survival model fitting to different image features were quantified by Akaike information criteria (AIC).

$$\text{AIC} = -2 \log(\text{likelihood}) + 2K$$

(11)

where likelihood is a measure-of-model fitness and $K$ represents the number of model parameters. The smaller value of the AIC, the better the goodness of fit of the survival models.

**Experimental Results**

In this section, we conducted the experiments on the public prostate cancer dataset to make statistical analysis on various survival models using different histopathological image feature quantification methods.

**Implementation details**

For the CNN-based approaches to extract image features, we first used the patches to train the CNN with multitask loss. Each patch was resized as $256 \times 256$ and assigned two labels according to the Gleason grading of the WSI: one being the primary pattern and another being the Gleason score. The CNN was trained with mini-batch stochastic gradient descent. The momentum is 0.9, and weight decay was $5 \times 10^{-5}$. The initial learning rate is $10^{-3}$ and annealed by 0.1 after 10 iterations. To train the LSTM, we set the same momentum, the weight decay, and the initial learning rate. The learning rate is annealed by 0.1 after $2 \times 10^3$ iterations. The implementation is based on the Caffe toolbox.

**Comparison of image features**

First, only using image features from tissue specimens, including clinical Gleason primary and secondary patterns and the quantified image features from various image methods, their Cox hazard ratios are shown in Table 3. CNN achieved better results than texture methods, including SURF, HOG, and LBP. Using CNN with LSTM to model the spatial relation of patches achieved the highest Cox hazard ratio, which indicated the best recurrence correlation for prostate cancer patients' recurrence data. On the other hand, the image features obtained from texture-based methods and CNN
Second, in addition to the image features, PSA levels, ages, and clinical tumor stages were included in the Cox survival model, besides the primary and the secondary Gleason patterns. The results of combining clinical factors and image features are shown in Table 4, demonstrating that the image features generated from CNN-based approaches were more representative than the texture features by having higher values of hazard ratio. In addition, those features were more representative than clinical prognostic factors. We also calculated the AIC values, as shown in Table 4. The smaller AIC value encodes the better goodness of fit of the survival model. CNN + LSTM achieved the best fitness on the Cox regression model compared to other image features quantification methods.

Finally, without any image features, we showed the Cox hazard ratios of the clinical factors, as shown in Table 5. From the results of Tables 3-5, we can see that primary Gleason patterns have higher Cox hazard ratios than the ones of other clinical factors, which was consistent with its high prediction power for prostate cancers.[14]

**Ablation study on training strategies**

Furthermore, considering the multiple Gleason patterns within WSIs, we designed two training strategies to train the CNN-based approaches. The first one was to use multitask loss to learn both the primary Gleason pattern and the sum of the primary and secondary patterns (namely, the Gleason score). The second one was to use the primary Gleason pattern or the Gleason score alone to learn the patterns within the patches or WSIs.

The performance of two CNN-based approaches on patient recurrence analysis was compared using different training strategies. The results are shown in Table 6. We can see that the multitask architecture achieved better correlation with patients’ recurrence than training label using the primary Gleason pattern or Gleason score alone as it has much higher recurrence hazard ratios and lower AIC values. This is because the primary Gleason pattern and the Gleason score together could better reflect the local and global image features in the WSIs than use each alone.

**Comparison of survival models**

In this section, we performed statistical analysis on various survival models, including COX-EN,[28] PH-EX,[50] PH-LogN,[30] and PH-LogL,[30] using prostate images with Gleason score 6–8 and clinical factors. The Cox proportional-hazards model does not need an assumption of a particular survival distribution of the patients’ survival data. The only assumption in the model is about the proportional hazards. Unlike the Cox proportional-hazards model, parametric models with different penalty distance functions (such as exponential, log-normal, and log-logistic) need to specify the hazard functions.[52,53] Studies have indicated that under certain circumstances, such as strong effect or strong time trend in covariates or follow-up depending on covariates, the parametric models are good alternatives to the Cox regression model.[53]

We assessed different survival models and show the hazard ratios of image features and patients’ clinical prognostic factors, as shown in Table 7. Based on these results, first, we can see that the image features quantified from WSIs outperformed other clinical factors in all texture and CNN-based approaches. Second, CNN-based approaches achieved a better correlation

| Table 3: The Cox hazard ratios of only using clinical Gleason primary and secondary patterns and image features from different image analysis methods |
| Methods | Primary pattern | Secondary pattern | Image features |
|--------|----------------|------------------|---------------|
| SURF   | 0.76           | 0.58             | 1.15          |
| HOG    | 0.84           | 0.55             | 1.09          |
| LBP    | 0.77           | 0.60             | 1.10          |
| CNN    | 0.80           | 0.73             | 1.83          |
| CNN + LSTM | 0.90       | 0.71             | 3.54          |

The texture feature quantification methods include SURF,[28] HOG,[28] and LBP.[28] Using CNN with LSTM to model the spatial relationship of patches achieves the highest Cox hazard ratio, which indicates the best performance on progression prediction for the recurrence data. Meanwhile the image features from texture and CNN approaches achieve the Cox hazard ratios compared to the ones from clinical Gleason primary and secondary patterns. SURF: Speeded-up robust features, HOG: Histogram of oriented gradient, CNN: Convolutional neural network, LSTM: Long-short-term memory.

| Table 4: The Cox hazard ratios and Akaike information criteria of using clinical factors including Gleason primary and secondary patterns, patients’ prostate-specific antigen, age, and clinical tumor stages, and image features from different image analysis methods |
| Methods | Primary pattern | Secondary pattern | PSA | Age | Tumor stage | Image features | AIC |
|--------|----------------|------------------|-----|-----|-------------|----------------|----|
| SURF   | 0.99           | 0.67             | 0.84| 0.98| 1.04        | 1.13           | 38.93|
| HOG    | 1.21           | 0.65             | 0.82| 1.01| 1.13        | 1.10           | 51.97|
| LBP    | 0.97           | 0.76             | 0.84| 1.00| 1.08        | 1.08           | 35.97|
| CNN    | 1.10           | 1.13             | 0.80| 1.00| 1.17        | 2.58           | 38.02|
| CNN + LSTM | 1.38      | 0.75             | 0.76| 0.97| 1.14        | 7.10           | 35.60|

The texture feature quantification methods include SURF,[28] HOG,[28] and LBP.[28] Using CNN + LSTM achieves the highest Cox hazard ratio and lowest value of AIC, which indicates the best performance on progression prediction for the recurrence data. PSA: Prostate-specific antigen, AIC: Akaike information criteria, SURF: Speeded-up robust features, HOG: Histogram of oriented gradient, LBP: Local binary pattern, LSTM: Long-short-term memory.
with patients’ recurrence due to their higher hazard ratios than other texture methods for all survival models. Third, by comparing with Table 4, COX-EN achieved the lowest AIC value with image features obtained from CNN + LSTM, proving that the model was more suitable for recurrence analysis for prostate patients with low, intermediate, and high risk than other survival models.

**Discussion and Conclusions**

**Table 5: The Cox hazard ratios of the clinical factors**

| Primary pattern | Secondary pattern | PSA | Age | Tumor stage |
|-----------------|-------------------|-----|-----|-------------|
| 2.15            | 1.09              | 0.73| 0.90| 1.30        |

PSA: Prostate-specific antigen

**Table 6: The Cox hazard ratios and Akaike information criteria of convolutional neural network-based approaches on patients’ progression analysis using three different training strategies**

| Methods | Training Strategy | Primary Pattern | Secondary Pattern | PSA | Age | Tumor Stage | Image Features | AIC |
|---------|-------------------|-----------------|-------------------|-----|-----|-------------|----------------|-----|
| CNN     | Primary Pattern   | 1.11            | 1.12              | 0.80| 1.00| 1.16        | 1.34           | 46.13|
| CNN     | Gleason Score     | 1.26            | 1.03              | 0.75| 0.98| 1.12        | 1.53           | 44.29|
| CNN     | Multi-task        | 1.10            | 1.13              | 0.80| 1.00| 1.17        | 2.58           | 38.02|
| CNN + LSTM | Primary Pattern | 1.35            | 0.84              | 0.78| 0.98| 1.14        | 1.63           | 44.27|
| CNN + LSTM | Gleason Score | 1.09            | 0.66              | 0.81| 0.99| 1.11        | 2.76           | 41.47|
| CNN + LSTM | Multi-task      | 1.38            | 0.75              | 0.76| 0.97| 1.14        | 7.10           | 35.60|

Using multitask architecture achieves the highest Cox hazard ratio and lowest AIC values than training using the primary Gleason pattern or Gleason score alone, which indicates the best performance on progression prediction for the recurrence data. CNN: Convolutional neural network, LSTM: Long-short-term memory, PSA: Prostate-specific antigen, AIC: Akaike information criteria.

**Table 7: The Cox hazard ratios and Akaike information criteria of different survival models using texture methods and convolutional neural network-based approaches**

| Survival models | Methods | Primary patterns | Secondary patterns | PSA | Age | Tumor stage | Image features | AIC |
|-----------------|---------|------------------|--------------------|-----|-----|-------------|----------------|-----|
| COX-EN          | SURF    | 0.10             | 0.27               | 0.33| 0.06| 0.03        | 3.38           | 42.93|
| COX-EN          | HOG     | 0.10             | 0.25               | 0.32| 0.06| 0.03        | 3.85           | 59.72|
| COX-EN          | LBP     | 0.10             | 0.19               | 0.30| 0.06| 0.03        | 2.40           | 39.83|
| COX-EN          | CNN     | 0.23             | 0.21               | 0.33| 0.06| 0.04        | 7.57           | 29.86|
| COX-EN          | CNN + LSTM | 0.13          | 0.27               | 0.36| 0.06| 0.03        | 15.85          | 29.83|
| PH-EX           | SURF    | 0.07             | 0.09               | 0.29| 0.03| 0.03        | 1.94           | 41.26|
| PH-EX           | HOG     | 0.05             | 0.12               | 0.29| 0.04| 0.03        | 2.41           | 61.56|
| PH-EX           | LBP     | 0.07             | 0.06               | 0.28| 0.03| 0.03        | 1.49           | 42.12|
| PH-EX           | CNN     | 0.08             | 0.07               | 0.29| 0.04| 0.04        | 4.50           | 35.60|
| PH-EX           | CNN + LSTM | 0.08              | 0.10               | 0.29| 0.04| 0.04        | 10.22          | 31.22|
| PH-LogN         | SURF    | 0.18             | 0.22               | 0.30| 0.02| 0.08        | 2.03           | 47.27|
| PH-LogN         | HOG     | 0.18             | 0.23               | 0.30| 0.02| 0.08        | 2.70           | 47.58|
| PH-LogN         | LBP     | 0.21             | 0.18               | 0.29| 0.02| 0.08        | 1.38           | 45.99|
| PH-LogN         | CNN     | 0.16             | 0.15               | 0.30| 0.02| 0.08        | 4.33           | 42.51|
| PH-LogN         | CNN + LSTM | 0.20             | 0.18               | 0.31| 0.02| 0.08        | 11.92          | 33.31|
| PH-LogL         | SURF    | 0.11             | 0.15               | 0.29| 0.02| 1.89        | 1.89           | 43.74|
| PH-LogL         | HOG     | 0.07             | 0.20               | 0.28| 0.02| 2.91        | 2.91           | 44.45|
| PH-LogL         | LBP     | 0.79             | 0.29               | 1.09| 0.77| 1.46        | 1.46           | 44.39|
| PH-LogL         | CNN     | 0.09             | 0.08               | 0.29| 0.03| 4.39        | 4.39           | 35.96|
| PH-LogL         | CNN + LSTM | 0.12              | 0.13               | 0.29| 0.02| 9.92        | 9.92           | 33.02|

The survival models include COX-EN, PH-EN, PH-LogN, and PH-LogL. CNN: Convolutional neural network, LSTM: Long-short-term memory, PSA: Prostate-specific antigen, AIC: Akaike information criteria, SURF: Speeded-up robust features, HOG: Histogram of oriented gradient, LBP: Local binary pattern.

In this paper, we presented three unsupervised texture methods (SURF, HOG, and LBP) and two supervised CNN-based methods to quantify the features from histopathological images. Five survival models were assessed on those image features along with prostate cancer clinical prognostic factors, including the primary and the secondary Gleason patterns, PSA, age, and clinical tumor stage to perform bPFS analyses.

Based on the statistical comparisons among different image feature quantification methods with survival models, the CNN-LSTM provided the highest hazard ratio of prostate cancer recurrence under COX-EN. COX-EN outperforms other image quantification methods with other survival models, respectively. In our approach, patient outcomes were better correlated with their histopathological image features.
to the limited size of the public prostate dataset, the results achieved from our experiments were preliminary. To further validate its generalizability of our approach, more prostate images from local institutions are needed to perform extensive experiments.

In the future, besides using tissue WSIs for patients’ bRFS analysis, integrating patients’ genomic information and tissue histopathology images will be investigated as a means for providing additional predictive power. Doing so would provide a more quantitative and accurate clinical decision-making support system for patients with prostate cancer.

Financial support and sponsorship
This research was funded, in part, by grants from NIH contracts 4R01LM009239-08, 4R01CA161375-05, 1UG3CA225021-01, and P30CA072720.

Conflicts of interest
Dr. Singer is the principal investigator on an investigator-initiated clinical trial that is funded by Astellas/Medivation (NCT02885649) (http://cjin.org/clinical-trials/index?show=trial&p=081604). The other authors declare that they have no competing interests.

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