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Deep Neural Networks with Prior Evidence for Bladder Cancer Staging

Xiaoqian Zhou

*School of Computer Eng. and Sci.
Shanghai University
Shanghai, China
zhouxiaoqian@shu.edu.cn*

Xiaodong Yue*

*School of Computer Eng. and Sci.
Artificial Intelligence Institute of Shanghai University
Shanghai University, China
yswantfly@shu.edu.cn*

Zhikang Xu

*School of Computer Eng. and Sci.
Shanghai University
Shanghai, China
xuzhikangba@shu.edu.cn*

Thierry Denoeux

*Sino-European School of Technology
Shanghai University, China
Université de technologie de Compiègne, Compiègne, France
thierry.denoeux@utc.fr*

Yufei Chen

*College of Electronics and Information Engineering
Tongji University
Shanghai, China
yufeichen@tongji.edu.cn*

Abstract—Bladder cancer staging is crucial for operation planning and cancer assessment. Deep Convolutional Neural Networks (DCNNs) have been widely used to classify the bladder tumor images to identify cancer stages. However, the pure image-based deep learning methods over depend on the labeled data training and neglect the clinical priors. Human doctors judge the stage of a bladder tumor through checking whether the tumor infiltrating into bladder wall. The clinical priors of tumor infiltration are helpful to improve the DCNN-based bladder cancer staging and make the predictions coincide with the law of medicine. To involve clinical priors into deep learning for cancer staging, we propose a DCNN model with prior evidence to classify medical images of bladder tumors. Specifically, we measure the degree of tumor infiltrating into bladder wall to construct the prior evidence and integrate the prior evidence into the image-based prediction with evidential deep neural networks. We analyze the learning objective and prove that the prior evidences consistent with the ground truth will certainly reduce the prediction error and variance produced by image-based neural networks. The experiments on bladder cancer MR images datasets validate that involving prior evidences is effective to improve the DCNN-based cancer staging.

Index Terms—bladder cancer staging, evidential deep neural network, prior evidence

I. INTRODUCTION

Radiographs such as Magnetic Resonance (MR) and Computed Tomography (CT) images are crucial for diagnosis and treatments of bladder cancer. As to the superiority of image feature extraction, Deep Convolutional Neural Networks (DCNNs) have been widely used in the image-based Computer Aided Diagnosis (CAD) of bladder cancer [1], [2], which include cancer staging [3], [4], tumor segmentation [5]–[7], cancer treatments [8], [9] and etc. Bladder cancer staging is generally performed based on MR images. Based on the characteristics of tumors in images, the bladder tumors can be staged from T0 to T4 and the tumors of T2 or greater stages are often treated with partial or total cystectomy [10].

For bladder cancer staging, most existing methods directly utilize deep neural networks to classify bladder images of

patients to determine the stage to tumors. However, the pure image-based classification methods over depend on the model training on labeled image data and neglect the clinical experiences and priors. Human doctors generally judge the stage of a bladder tumor through checking whether the tumor infiltrating into bladder wall. The clinical priors of tumor infiltration are helpful to improve the prediction accuracy of cancer stage and make the predictions coincide with the law of medicine.

To involve clinical priors into deep learning for cancer staging, we propose a deep convolutional neural network with prior evidence to classify the MR images of bladder tumors. Specifically, we construct the prior evidence of tumor infiltrating into bladder wall and integrate the prior evidence into the image-based prediction with evidential deep neural networks. Figure 1 illustrates the workflow of the proposed method. The block of green dash line indicates the image-based prediction, which can be considered as a process of DCNNs extracting evidences from images for prediction. The block marked with orange dash line shows the process of generating prior evidences of tumor infiltration. Through fusing the evidences from both image data and priors, we formulate the probability distribution of prediction with both prior and image data. Based on the probability distribution of prediction, we construct the loss objective of evidential deep neural network to involve priors into DCNNs for cancer stage identification. The contributions of the paper work are summarized below.

- *Propose an intuitive way to construct the prior evidence of tumor infiltration to formulate clinical experience.* The prior evidence of tumor infiltrating into bladder wall is measured by the overlap degree between the segmentation masks of tumor and wall, which can be efficiently computed based on the inner product of mask matrices.
- *Propose an evidential deep neural network with prior evidence of tumor infiltration for bladder cancer staging.*

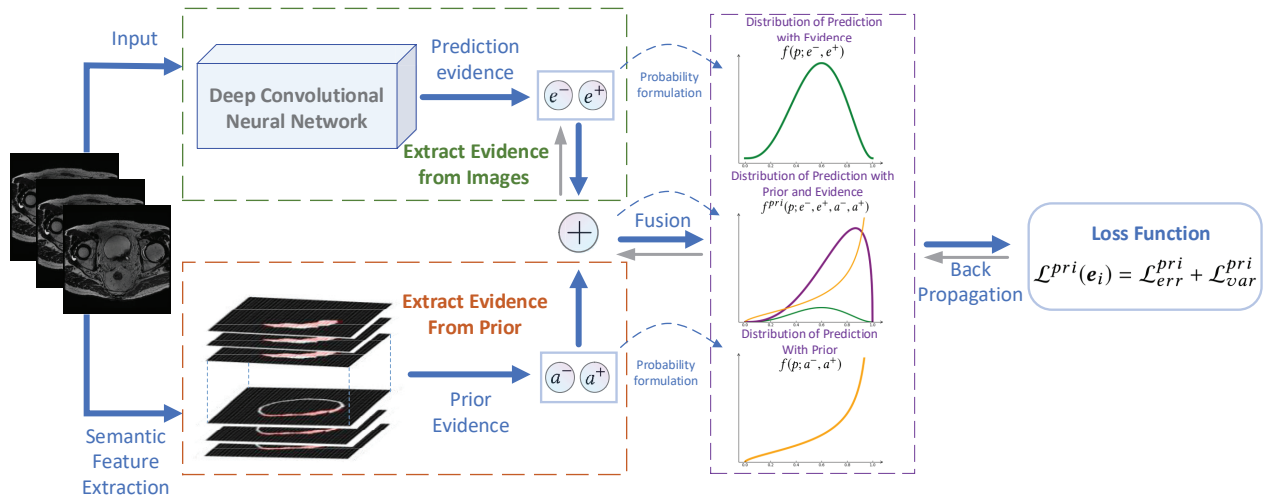


Fig. 1. Workflow of bladder cancer staging.

We formulate the prior probability distribution with prior evidence and fuse the prior probability into the objective of evidential deep neural networks built on only labeled images. We analyze the learning objective and prove that the prior evidences consistent with the ground truth will reduce the prediction errors produced by image-based neural networks.

II. RELATED WORK

A. Computer-aided diagnosis of bladder cancer

Deep Convolutional Neural Networks (DCNNs) are good at extracting hierarchical features from images at multiple levels of image abstraction [11], [12]. As to the superiority of image feature learning, DCNNs have been widely utilized to implement Computer-Aided Diagnosis systems of bladder cancer based on medical images. The applications include bladder cancer staging, bladder segmentation [13], tumor detection [14] and cancer treatments.

In the applications of bladder segmentation, tumor detection and cancer treatments, Ma et al. proposed an automated bladder segmentation method based on U-Net for CT urography, in which the bladder boundary is estimated by U-Net without user-input bounding box [15]. Shkolyar et al. built up CystoNet based on DCNNs to improve the localization, surgical resection and intraoperative navigation of bladder tumors [16]. Rundo et al. proposed a radionics pipeline to describe possible responses of bladder cancer patients during immunotherapeutic treatments [17].

For bladder cancer staging, DCNNs were utilized to extract features from MR images to recognize the stage of bladder tumors. Garapati et al. used DCNNs to segment bladder lesions from MR images to extract morphological features and adopted the LDA classifier to predict bladder cancer stage [3]. Moreover, the morphological and texture features were synthesized and various kinds of classifiers which include Support Vector Machine, Neural Network, Random Forest were also utilized to improve the cancer staging predictions

[4]. Besides image feature extraction, Zhang et al. learnt bladder cancer staging rules from MR images referring to clinical experiences and integrated the rules into DCNNs for tumor stage classification [18].

B. Machine learning based on evidence theory

Evidence theory (Dempster-Shafer evidence theory) is regarded as a kind of generalized probability. Evidence theory utilizes mass function to measure the uncertainty in decision-making and performs reasoning by Dempster's rule [19], [20]. Evidence theory has been widely used in the fields of information fusion and reasoning with uncertainty. Combining evidence theory with machine learning, related researches have implemented a variety of supervised learning and unsupervised learning algorithms for uncertain data analysis, which includes Evidential K-Nearest Neighbors [21], Evidential Linear Discrimination Analysis [22], BP neural network with evidence [23] and etc.

Evidence theory has been widely used in medical image analysis, such as medical image segmentation. Capelle et al. presented a region-based segmentation method for the detection of brain tumors in which each voxel's segmentation in MR images is combined with its neighborhood information by using Dempster's rule [24]. Lian et al. proposed a multi-modality medical image segmentation method, using belief functions to formulate the uncertain and imprecise segmentation in each modality, and utilized Dempster's rule to fuse segmentation results of different modalities [25]. Huang et al. used belief functions to evaluate the segmentation uncertainty of boundary regions, and adopted Dempster's rule to fuse it with output probabilities of segmentation [26]. Besides image segmentation, evidence theory was also used for other tasks of medical image analysis. In recent years, some researchers combined evidence theory with deep learning and proposed evidential deep neural networks to improve the ability of evidence theory to process complex data [27]. In the evidential deep neural networks, evidence theory is used to measure

the uncertainty of the predictions produced by deep neural networks and rectify the unreasonable predictions [28].

III. DCNN WITH PRIOR EVIDENCE FOR BLADDER CANCER STAGING

A. Constructing prior evidence of tumor infiltration

As introduced in Section I, the stage of bladder cancer can be divided into five phases from T0 to T4. The stages greater than T2 are considered as high stages and require cystectomy [10]. According to the clinical experience, human doctors generally identify the stage of bladder tumors through checking the degree of tumor infiltrating into bladder wall. It is intuitive to consider that the high overlap degree between the regions of tumor and bladder wall indicates the high cancer stage ($\geq T2$), conversely, the low overlap degree indicates the low stage ($< T2$). Therefore, we can compute the overlap degree between tumor and bladder wall as the prior evidence of tumor infiltration,

$$\varrho = \frac{\langle M_{tumor}, M_{wall} \rangle}{\|M_{wall}\|_2^2}, \quad (1)$$

where M_{tumor} and M_{wall} denote the mask matrixes of tumor and bladder wall segmented from MR images respectively, $\langle \cdot, \cdot \rangle$ is the Frobenius inner product of two matrixes. For each image i , we further normalize the overlap degree ϱ_i to $\rho_i = \frac{\varrho_i - \varrho^{min}}{\varrho^{max} - \varrho^{min}}$. Two instances in Figure 2 show the correlation between the tumor-wall overlap degree and the bladder cancer stage. As ρ increases, the predicted bladder cancer stage will increase from $< T2$ to $\geq T2$. In the next section, we compute the prior evidence of tumor infiltration for each image based on ρ_i to improve the performance of bladder cancer staging.

B. Involving prior evidence into DCNN to identify cancer stage

As mentioned in Section II-B, in the evidential deep neural network (EvidentialNet) [28], the network prediction \mathbf{p} is extended to a *Binomial* probability distribution and the probability density function (*pdf*) of the prediction \mathbf{p} is denoted as $f(\mathbf{p}; e^-, e^+)$. e^-, e^+ are the model outputs of DCNN which are considered as the prediction evidences extracted from images to support stage $< T2$ and stage $\geq T2$ respectively. In contrast to the image-based prediction, we formulate the prediction based on priors with *Beta* distribution and suppose the *pdf* of the prediction is $f(\mathbf{p}; a^-, a^+)$ where a^-, a^+ are the prior evidences of tumor infiltration to support stage $< T2$ and stage $\geq T2$ respectively. According to Bayesian theorem, we can formulate the *pdf* of the prediction based on both image data and priors as

$$f^{pri}(\mathbf{p}; e^-, e^+, a^-, a^+) = f(\mathbf{p}; e^-, e^+) * f(\mathbf{p}; a^-, a^+). \quad (2)$$

For each image i , we further infer the *pdf* and obtain

$$f^{pri}(\mathbf{p}_i; e_i^-, e_i^+, a_i^-, a_i^+) = \frac{p_{i0}^{e_i^- + 2a_i^- - 1} p_{i1}^{e_i^+ + 2a_i^+ - 1}}{\mathcal{B}(e_i^+ + 2a_i^+, e_i^- + 2a_i^-)}, \quad (3)$$

where $\mathbf{p}_i = (p_{i0}, p_{i1})$, and p_{i0} and p_{i1} are the prediction probabilities belonging to stage $< T2$ and stage $\geq T2$, respectively.

$\mathcal{B}(\cdot)$ denotes *Beta* function. Based on the tumor-wall overlap degree in Section III-A, we can calculate the prior evidences a_i^-, a_i^+ as the parameters of f^{pri} by

$$a_i^- = 1 - \rho_i, \quad a_i^+ = \rho_i. \quad (4)$$

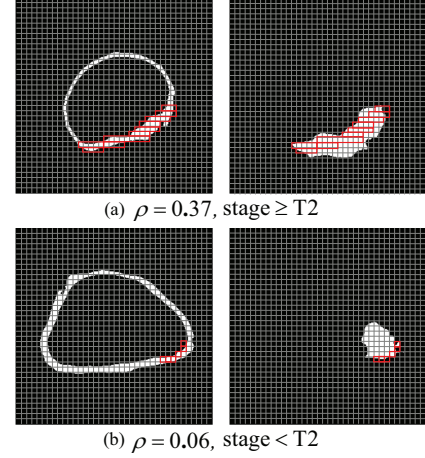


Fig. 2. Calculation of prior evidence from segmentations.

Based on the *pdf* of the prediction based on both image data and priors, we can construct the expectation of the prediction error as the loss objective of the deep neural network with prior. Given a data set $\mathcal{D} = \{x_i, \mathbf{y}_i\}_{i=1}^N$ of N labeled images, suppose $\mathbf{y}_i = (y_{i0}, y_{i1})$ is the one-hot label vector for x_i , $\mathbf{y}_i = (0, 1)$ when stage $\geq T2$ and $\mathbf{y}_i = (1, 0)$ when stage $< T2$. The prediction loss of the i th image is

$$\begin{aligned} \mathcal{L}^{pri}(e_i) &= \int \|\mathbf{y}_i - \mathbf{p}_i\|_2^2 f^{pri}(\mathbf{p}_i; e_i^+, e_i^-, a_i^+, a_i^-) d\mathbf{p}_i \\ &= E_{f^{pri}} [\|\mathbf{y}_i - \mathbf{p}_i\|_2^2] \\ &= \sum_{j=0}^1 E_{f^{pri}} [y_{ij}^2 - 2y_{ij}p_{ij} + p_{ij}^2] \\ &= \sum_{j=0}^1 (y_{ij}^2 - 2y_{ij}E_{f^{pri}}(p_{ij}) + E_{f^{pri}}(p_{ij}^2)). \end{aligned} \quad (5)$$

Because $E_{f^{pri}}(p_{ij}^2) = E_{f^{pri}}(p_{ij})^2 + Var_{f^{pri}}(p_{ij})$, we infer the formula and obtain

$$\begin{aligned} \mathcal{L}^{pri}(e_i) &= \sum_{j=0}^1 (y_{ij} - E_{f^{pri}}(p_{ij}))^2 + Var(p_{ij}) \\ &= \underbrace{\left(y_{i0} - \frac{e_i^- + 2a_i^-}{S_i} \right)^2 + \left(y_{i1} - \frac{e_i^+ + 2a_i^+}{S_i} \right)^2}_{\mathcal{L}_{err}^{pri}} \\ &\quad + \underbrace{\frac{2(e_i^- + 2a_i^-)(e_i^+ + 2a_i^+)}{S_i^2(S_i + 1)}}_{\mathcal{L}_{var}^{pri}}, \end{aligned} \quad (6)$$

where $S_i = e_i^- + e_i^+ + 1$. From (6), we know that the prediction loss of neural network consists of two terms. The first term \mathcal{L}_{err}^{pri} denotes the prediction error (bias) and the second term \mathcal{L}_{var}^{pri} represents the variance of predictions. This reveals that we can reduce both the prediction error and variance through minimizing the loss function. Moreover, we can obtain the

following theorems to analyze the prediction enhancement brought by priors.

Theorem 1. For positive instances, if prior evidences $a^+ > a^-$, we have $\mathcal{L}_{err} > \mathcal{L}_{err}^{pri}$. For negative instances, if $a^- > a^+$, $\mathcal{L}_{err} > \mathcal{L}_{err}^{pri}$.

proof: Without priors, we can obtain the predictive error term \mathcal{L}_{err} of EvidentialNet as

$$\mathcal{L}_{err} = \left(y_0 - \frac{e^- + 1}{\mathcal{S}}\right)^2 + \left(y_1 - \frac{e^+ + 1}{\mathcal{S}}\right)^2. \quad (7)$$

In contrast, the predictive error term with prior \mathcal{L}_{err}^{pri} in (6) is

$$\mathcal{L}_{err}^{pri} = \left(y_0 - \frac{e^- + 2a^-}{\mathcal{S}}\right)^2 + \left(y_1 - \frac{e^+ + 2a^+}{\mathcal{S}}\right)^2. \quad (8)$$

Because $a^+ > a^-$, $a^+ + a^- = 1$, we have $e^- + 2a^- < e^- + 1$ and $e^+ + 2a^+ > e^+ + 1$. According to (7) and (8), we can infer that

$$\begin{aligned} \left(y_0 - \frac{e^- + 1}{\mathcal{S}}\right)^2 &> \left(y_0 - \frac{e^- + 2a^-}{\mathcal{S}}\right)^2, \\ \left(y_1 - \frac{e^+ + 1}{\mathcal{S}}\right)^2 &> \left(y_1 - \frac{e^+ + 2a^+}{\mathcal{S}}\right)^2, \\ \mathcal{L}_{err} &> \mathcal{L}_{err}^{pri}. \end{aligned} \quad (9)$$

For negative instances, we can make the similar proof.

Theorem 2. For each instance, if $(e^+ - e^-)(a^+ - a^-) > 0$, we have $\mathcal{L}_{var} > \mathcal{L}_{var}^{pri}$.

proof: The prediction variance term \mathcal{L}_{var} of EvidentialNet without priors is

$$\mathcal{L}_{var} = \frac{2(e^- + 1)(e^+ + 1)}{\mathcal{S}^2(\mathcal{S} + 1)}. \quad (10)$$

According to the prediction variance term with priors \mathcal{L}_{var}^{pri} in (6), we have

$$\begin{aligned} \mathcal{L}_{var} - \mathcal{L}_{var}^{pri} &= \frac{2(e^- + 1)(e^+ + 1)}{\mathcal{S}^2(\mathcal{S} + 1)} - \frac{2(e^- + 2a^-)(e^+ + 2a^+)}{\mathcal{S}^2(\mathcal{S} + 1)} \\ &= \frac{e^+(1 - 2a^-) + e^-(1 - 2a^+) + (1 - 4a^+a^-)}{\mathcal{S}^2(\mathcal{S} + 1)}. \end{aligned}$$

Because $(1 - 4a^+a^-) > 0$ and $a^+ + a^- = 1$, we have

$$\mathcal{L}_{var} - \mathcal{L}_{var}^{pri} = \frac{(e^+ - e^-)(a^+ - a^-) + (1 - 4a^+a^-)}{\mathcal{S}^2(\mathcal{S} + 1)} > 0. \quad (11)$$

Referring to Theorem 1, we can design a strategy to determine whether a prior can be integrated into DCNN-based classification and thereby filter out prior evidences to guarantee the decrease of prediction error. From Theorem 2, we know that when the prediction evidences for classification are consistent with the prior evidences, the variance of the prediction produced by DCNNs will be reduced.

IV. EXPERIMENT RESULTS

In the experiments, the bladder cancer MR images for stage prediction are collected from two sources, our cooperative hospital and Chinese University Computer Design Competition. The image data set contains 344 MR images of 38 patients, and the size of MR images is 512×512 . All the MR images are labeled with high cancer stage (stage $\geq T2$) or low cancer

stage (stage $< T2$) by human doctors and the ratio between high stage and low stage is 1.26 : 1.

We divide the data set by patients and conduct five-fold cross validation to implement experiments. Moreover, we employ the measures of *accuracy*, *precision*, *recall rate* and *F1-score* to evaluate the performances of image classification methods. The experiments include two tests. The first test will verify that integrating prior evidence into DCNNs is effective to improve the predictions of bladder cancer stage. The second test will validate the superiority of the proposed method through comparing with other representative image classification methods.

A. Validation of prior evidence for prediction improvement

In this test, we implement ablation studies to verify the prediction improvement brought by integrating prior evidences of tumor infiltration into DCNN. We adopt ResNet [29], EvidentialNet [28], and our method in which the prior evidence of tumor infiltration is integrated into EvidentialNet to classify the bladder MR images for cancer staging. All the deep neural networks above are constructed based on the backbone network model of ResNet18 [29]. The classification results are presented in Table I. We can find that based on the evidential representation of prediction, EvidentialNet achieves more precise predictions than ResNet. If we integrate priors into EvidentialNet (denoted as EvidentialNet+prior), all the evaluation measures of *accuracy*, *precision*, *recall rate* and *F1-score* are further improved by +8.91%, +11.44%, +4.96% and +8.35%, which verifies the prediction improvement of prior integration.

TABLE I
ABLATION STUDIES OF INTEGRATING PRIOR EVIDENCE

	ResNet	EvidentialNet	EvidentialNet+prior (Our Method)
<i>Accuracy</i>	72.14	83.86	92.77
<i>Precision</i>	70.43	80.40	91.84
<i>Recall</i>	84.19	90.05	95.01
<i>F1-score</i>	76.06	84.84	93.19

Next we exemplify integrating priors of tumor infiltration is helpful for DCNNs to identify the confusing cases of cancer staging. Figure 3 presents four cases that are misclassified by EvidentialNet but correctly identified by EvidentialNet+prior.

As shown in Figure 3(a), the contour and intensities of shaded area in the red circle are similar to the bladder tumor, which causes EvidentialNet to generate misclassification of stage $\geq T2$. In contrast, involving the prior evidence of tumor infiltration in model training, our method can extract the evidence of non-tumor-infiltration and integrate it into deep neural networks, which enhances the low stage prediction of $p_0 = 0.30$ produced by EvidentialNet to $p_0 = 0.86$ and rectifies the prediction. The shade impact also occurs in Figure 3(b). Guided by the prior evidence learnt from segmentation masks, our method enhances the prediction of low stage $p_0 = 0.24$ produced by EvidentialNet to $p_0 = 0.77$ to improve the prediction.

In Figure 3(c) and (d), because the intensities of tumor are similar to bladder wall, the EvidentialNet based on only image

data may be confused and generate wrong decisions of low cancer stage. In contrast, involving the prior evidences learnt from segmentation masks in training phase, our method can extract the evidences of tumor infiltration and improve the prediction $p_1 = 0.76$, $p_1 = 0.35$ produced by EvidentialNet to $p_1 = 0.88$, $p_1 = 0.93$ and generate the correct predictions of high cancer stage.

According to the results of the ablation experiment, we validate that integrating prior evidence of tumor infiltration into DCNNs is helpful to recognize the confusing cases and thereby improve the tumor stage predictions.

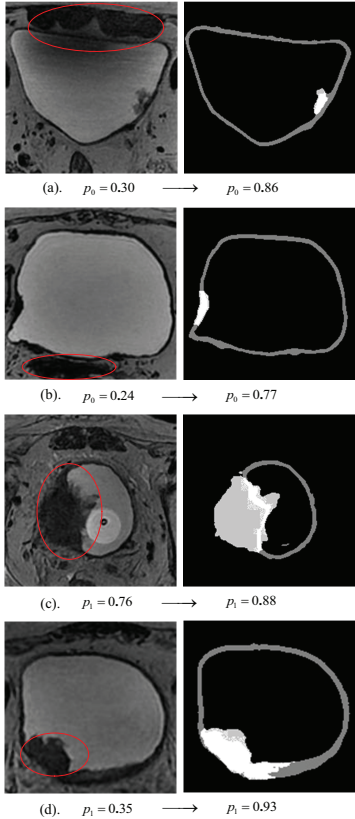


Fig. 3. Confusing cases of bladder cancer staging. Left column presents the original MR images and the cancer stage predictions produced by EvidentialNet. Right column presents the corresponding bladder wall and tumor regions in MR images and the predictions produced by EvidentialNet+prior.

B. Comparison with other bladder cancer staging methods

To validate the effectiveness of our method, we compare our method with four state-of-the-art DCNN-based medical image classification methods including ResNet18 [29], DenseNet [30], EvidentialNet [28] and another prior-integrated DCNN method RuleNet [18]. Figure 4 and Table II present the comparison of cancer stage classification results produced by different methods.

We can find that the proposed method achieves the best performance in terms of all the evaluation metrics. The prior integration can make the DCNN prediction of cancer stage more precise and stable. As shown in Figure 4, through integrating priors, the proposed method and RuleNet outperform the pure data-driven DCNN models of ResNet, DenseNet and EvidentialNet. Because the RuleNet requires sufficient data

to train an additional network to learn the decision rules of priors, our method achieves better performance than RuleNet on limited training data. Moreover, according to Theorem 1 and 2, the strategy of filtering prior evidences can guarantee that the integrated priors will reduce the prediction error and variance to produce more precise and stable prediction.

TABLE II
BLADDER CANCER STAGING PREDICTIONS GENERATED BY DIFFERENT METHODS.

Methods	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	72.14	70.43	84.19	76.06
<i>DenseNet</i>	78.80	75.43	87.19	80.87
<i>EvidentialNet</i>	83.86	80.84	90.05	84.84
<i>RuleNet</i>	85.24	83.68	91.08	86.80
<i>Our Method</i>	92.77	91.84	95.01	93.19

To further verify the DCNN prediction improvement brought by integrating prior evidence, we use Grad-CAM [31] to visualize the Regions Of Interests (ROIs) in MR images produced by different classification methods. The visualization of ROIs is shown in Figure 5.

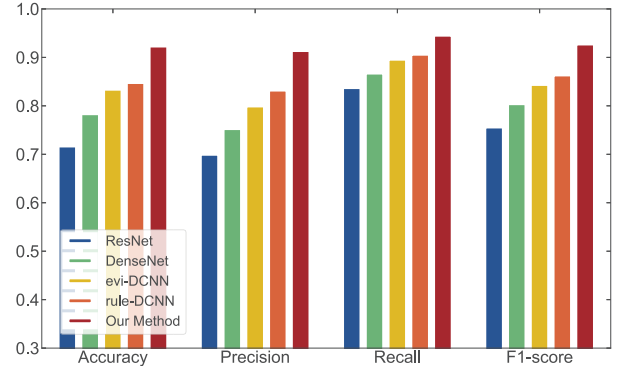


Fig. 4. Comparison of cancer staging methods.

We can find that ROIs of ResNet and DenseNet include the areas unrelated to bladder tumors and erratically distribute in MR images. The possible reason is that limited labeled MR images cannot guarantee the DCNNs to focus on the critical regions of bladder wall and tumor, such as contour and shape. Compare with these two methods, EvidentialNet can partially alleviate the data deficiencies by using evidence representation to implement classification. However, the predictive performances of EvidentialNet are not stable and it still includes unrelated areas when the contour and intensities of these areas are similar to bladder tumor. Through integrating the priors of logic rules, RuleNet generates more precise and stable ROIs than data-driven network models, but it is sensitive to the noise in background areas. By extracting prior evidence from segmentation masks, the ROIs produced by our method can represent the overlapping areas between bladder tumor and wall, and are robust to the noise in the background. In summary, the visualization of ROIs indicates that integrating prior evidences of clinical experience is helpful to guide DCNNs to focus on the critical regions between bladder tumor and wall to improve the cancer stage prediction.

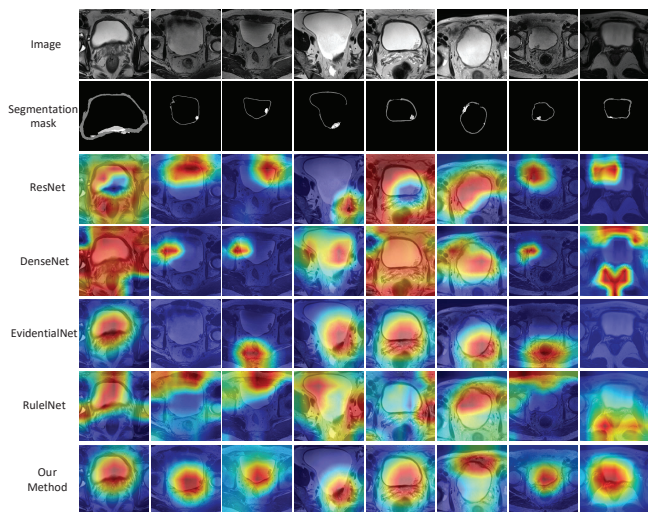


Fig. 5. Visualization of ROIs in MR images produced by comparative classification methods.

V. CONCLUSION

The bladder cancer staging methods using deep neural networks neglect clinical priors and may lead to irrational predictions. To tackle the problems, we propose an efficient way to construct the prior evidence of tumor infiltration to formulate clinical experience, and fuse the prior evidence into the evidential deep neural networks to improve the cancer stage prediction. The experiments validate the effectiveness of the proposed deep neural network with prior evidence for bladder cancer staging. The conflict between the prediction of neural networks and priors will be investigated in future work.

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