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PENet: Prior Evidence Deep Neural Network for Bladder Cancer Staging

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Abstract

Bladder cancer is a heterogeneous, complicated, and widespread illness with high rates of morbidity, death, and expense if not treated adequately. The accurate and exact stage of bladder cancer is fundamental for treatment choices and prognostic forecasts, as indicated by convincing evidence from randomized trials. The extraordinary capability of Deep Convolutional Neural Networks (DCNNs) to extract features is one of the primary advantages offered by these types of networks. DCNNs work well in numerous real clinical medical applications as it demands costly large-scale data annotation. However, a lack of background information hinders its effectiveness and interpretability. Clinicians identify the stage of a tumor by evaluating whether the tumor is muscle-invasive, as shown in images by the tumor's infiltration of the bladder wall. Incorporating this clinical knowledge in DCNN has the ability to enhance the performance of bladder cancer staging and bring the prediction into accordance with medical principles. Therefore, we introduce PENet, innovative prior evidence deep neural network, for classifying MR images of bladder cancer staging in line with clinical knowledge. To do this, first, the degree to which the tumor has penetrated into the bladder wall is measured to get prior distribution parameters of class probability called

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prior evidence. Second, we formulate the posterior distribution of class probability according to Bayesian Theorem. Last, we modify the loss function based on posterior distribution of class probability which parameters include both prior evidence and prediction evidence in the learning procedure. Our investigation reveals that the prediction error and the variance of PENet may be reduced by giving the network prior evidence that is consistent with the ground truth. Using MR image datasets, experiments show that PENet performs better than image-based DCNN algorithms for bladder cancer staging.

Keywords: Bladder cancer staging, deep neural network, prior evidence fusion

1. Introduction

Bladder cancer is a varied, complicated, and widespread illness with a changeable natural history that, if not treated adequately, is linked with high morbidity, fatality rates, and expense[1, 2]. Bladder cancer continues to evolve into two distinct subtypes, producing non-muscle-invasive tumors and non-papillary muscle-invasive tumors[3]. Complete excision of the tumor is the most frequent treatment for non-muscle-invasive bladder cancer (NMIBC), while radical cystectomy and neoadjuvant chemotherapy are the most common curative procedures for muscle-invasive bladder cancer (MIBC)[1]. Currently, the TNM staging system is the most prevalent tumor staging system and the standard approach for doctors to stage malignant tumors. NMIBC and MIBC correlate to T1 or less and T2 or more for bladder cancer T staging. Therefore, accurate and exact bladder cancer staging is extremely important, since it influences the treatment strategy and prognosis. Radiographs, such as those produced by magnetic resonance imaging (MRI) and computed tomography (CT), are the primary diagnostic tools and treatment modalities used in clinical settings to diagnose and treat of bladder cancer. As is well-known, DCNN has strong feature extraction capabilities and a promising future in clinical medical imaging, such as computer-aided diagnosis (CAD) of bladder cancer based on images[4], which covers cancer staging[5, 6], tumor segmentation[7, 8, 9], cancer treatments[10, 11], among others. Most known image-based approaches for staging bladder cancer rely on direct DCNNs to assess the stage of tumors based on images of patients' bladders. However, pure image-based classification methods necessitate costly large-scale data annotation as a foundation and disregard clinical

experiences and priors, which may lead to inaccurate tumor stage predictions inconsistent with medical knowledge, thereby limiting performance and interpretability. In contrast, clinical physicians determine the stage of a bladder tumor by detecting whether or not the tumor has spread into the surrounding muscle, which is also referred to as tumor infiltration into the bladder wall. Particularly effective for enhancing bladder cancer staging predictions and bringing them into compliance with medical law is incorporating clinical priors of tumor infiltration into DCNN. In order to achieve the stage prediction of bladder cancer in line with clinical knowledge, we introduce a novel prior evidence deep neural network called PENet.

First, by measuring how much a bladder tumor has infiltrated the bladder wall, we may use evidence theory[12, 13] to estimate how much evidence there is to support our hypothesis. So the prior distribution parameters of class probability are obtained called prior evidence. Second, Bayesian Theorem are used to directly formulate posterior distribution of class probability by likelihood distribution from observation and prior distribution of class probability. Last, we reconstructed the objective function of the evidential deep neural network based on posterior distribution of class probability to improve the performance of PENet by integrating prior evidence guidance. The contributions of this study are outlined in the following paragraph.

- *Propose a straightforward strategy for quantifying clinical features of tumor penetration into the bladder wall to obtain prior distribution parameter.* It is possible to determine how much overlap exists between the tumor and the bladder wall by determining how many matrices of the tumor and the bladder wall are in the inner product of each other to generate prior evidence as prior distribution parameter.
- *Construct posterior distribution of class probability.* We formulate posterior distribution based on Bayesian Theorem according to likelihood distribution from observation and prior distribution where distribution parameters are extracted evidences from images and prior respectively.
- *Propose a PENet for classifying bladder cancer stage images.* We reformulate the objective function of evidential deep neural networks for PENet based on posterior distribution of class probability to optimize PENet’s weight parameters. As we proved, PENet’s prediction errors may be reduced when fused prior evidence compatible with ground truth.

The remaining sections are grouped as follows. In Section 2, we discuss the relevant work. Section 3 discusses our proposed DCNN-based bladder cancer staging technique PENet, including the representation of clinical prior evidence of bladder tumor infiltration and the approach for fusing the prior evidence into DCNN for bladder cancer staging. Section 4 contains the experimental data that support the efficiency of PENet in assessing the bladder cancer stage. Conclusion is presented in Section 5.

2. Related Work

2.1. Computer-aided bladder cancer diagnosis

Bladder cancer, one of the most frequent malignant tumors of the urinary system[14, 15], with significant rates of morbidity, mortality, and cost. Depending on the proper stage of bladder cancer, treatment options and expected prognosis will change[16]. The TNM staging system is currently the most common tumor staging system and is the standard method for clinicians to classify malignant tumors. A partial or total cystectomy is often used to treat tumors of T2 or higher (MIBC), which may be diagnosed by MR imaging and staged from T0 to T4 depending on whether the tumor is muscle-invasive or the degree of infiltration. DCNNs have seen widespread application as a method of computer-aided detection for bladder cancer due to their capacity to automatically extract hierarchical characteristics from images at varying degrees of image abstraction, which allows DCNNs to analyze images at varying levels of detail [17, 18]. Applications encompass bladder segmentation[19, 20], tumor detection[21], cancer therapies, and bladder cancer staging[5].

For bladder segmentation, Ma et al. suggested an automatic bladder segmentation approach based on U-Net for CT urography, where the bladder boundaries do not need user input for the bounding box and are estimated by U-Net[7]. Shkolyar et al. suggested CystoNet with DCNN to improve the performance of bladder tumor localization, surgical resection, and intraoperative navigation for tumor detection[22]. For cancer treatments, Rundo et al. developed a non-invasive prediction system comprised of a CT scan image pipeline and a radionics pipeline to characterize the expected response to immunotherapy, therefore informing physicians of treatment alternatives[23].

Characteristics were automatically retrieved from medical pictures to stage the bladder tumors using DCNNs for bladder cancer staging. [6] improved cancer staging prediction by combining morphological and textural

98 features specific to bladder staging with many classifiers, including support
 99 vector machines, neural networks, and random forests. Functional character-
 100 istics representing percentiles of the cumulative distribution function (CDF),
 101 morphological features representing radionics texture features, and morpho-
 102 logical features defining tumor shape were retrieved from T2W-MRI, and
 103 DW-MRI as input to neural networks for bladder cancer staging [24]. Zhang
 104 et al. learned infiltration criteria from MR images that are advantageous for
 105 tumor staging based on clinical experiences and used the rules into DCNN to
 106 increase performance[25]. Using ResNet structure, non-local attention, and
 107 image super-resolution processing, [26] developed a model with high perfor-
 108 mance for CT imaging-based bladder cancer staging.

109 *2.2. Evidence-theory-driven machine learning*

110 Evidence theory (Dempster-Shafer evidence theory) is viewed as a type of
 111 generalized probability that applies Dempster’s rule to reasoning while using
 112 the mass function to evaluate decision-making uncertainty[12, 13]. Through
 113 quantifying views and their uncertainty, evidence theory has been extensively
 114 employed in the areas of information fusion and reasoning with uncertainty.
 115 By merging evidence theory with machine learning, a number of supervised
 116 and unsupervised learning methods for uncertain data analysis have been
 117 developed, including evidence K-nearest neighbor[27], evidence linear dis-
 118 crimination analysis[28], and neural network with evidence[29].

119 A combination of evidence theory with medical image analysis, such
 120 as medical picture segmentation, has been made. By employing Demp-
 121 ster’s rule to combine data from each voxel’s vicinity in MR images, Capelle
 122 et al. suggested a region-based segmentation approach for brain tumor
 123 segmentation[30]. According to Lian et al., the problem of unclear and impre-
 124 cise segmentation in each modality may be addressed by applying Dempster’s
 125 rule to fuse the results of distinct modality segmentation[31]. Belief function
 126 and Dempster’s rule are used by Huang et al. to measure the uncertainty
 127 of segmentation in the border area and increase performance[32]. For the
 128 diagnosis of pneumonia from chest X-ray pictures, [33] applies the Dempster-
 129 Shafer theory to the fusion of five pre-trained convolutional neural networks,
 130 including VGG16, Xception, InceptionV3, ResNet50, and DenseNet201, and
 131 offers good detection performance. Evidence theory is used for a variety
 132 of additional activities in the medical image analysis process in addition to
 133 being used for the segmentation of medical images.

134 In order to increase the effectiveness of evidence theory in processing
135 complex data, several researchers have recently merged it with deep learn-
136 ing techniques to create evidential deep neural networks[34] that construct
137 classification uncertainty[35]. Unlike conventional deep neural networks, ev-
138 idential deep neural networks treat the activation values of the output layer
139 as evidences retrieved from the data for prediction, and the prediction of
140 the network is therefore extended to a probability distribution with evidence
141 parameters. As a result, evidential deep neural networks provide a method
142 for calculating the degree of uncertainty in deep neural network predictions
143 and correcting the inaccurate ones [36, 37].

144 3. Method

145 3.1. Workflow

146 Two major components of the proposed PENet are the measurement of
147 prior clinical experiences for bladder cancer staging and formulation of pos-
148 terior probability distribution of class probability based on Bayesian Theory
149 for bladder cancer staging. Three elements of PENet’s process are shown
150 in Figure 1. The first highlighted module with a green dashed line depicts
151 the process of creating tumor stage evidences (When we want to express two
152 types of evidence for high or low cancer stage, or two sources of evidence
153 for data and clinical experiences, we use the word "evidences".) from la-
154 beled MR images using a deep convolutional neural network. The second
155 module, shown by an orange dashed line, depicts the procedure for retriev-
156 ing prior evidence of tumor staging from segmentation masks. The third
157 module, shown by the purple dotted line, we can formulate likelihood dis-
158 tribution from observation using extracted evidence from images(viewed as
159 random variable) as parameter; Similarly, based on extracted prior evidence,
160 we formulate prior distribution of class probability. Through Bayesian The-
161 orem, the posterior distribution of class probability can be derived with two
162 sources evidence parameters which is the basis of loss function for PENet to
163 improve performance.

164 3.2. Evaluation of tumor infiltration’s clinical experiences

165 The stages of bladder cancer may be categorized into five phases, from
166 T0 to T4, as mentioned in Section 1. Cystectomy is necessary if the stage
167 is higher than T2, which is considered a high stage[3]. The degree of tumor
168 infiltration into the bladder wall is a common way for human physicians to

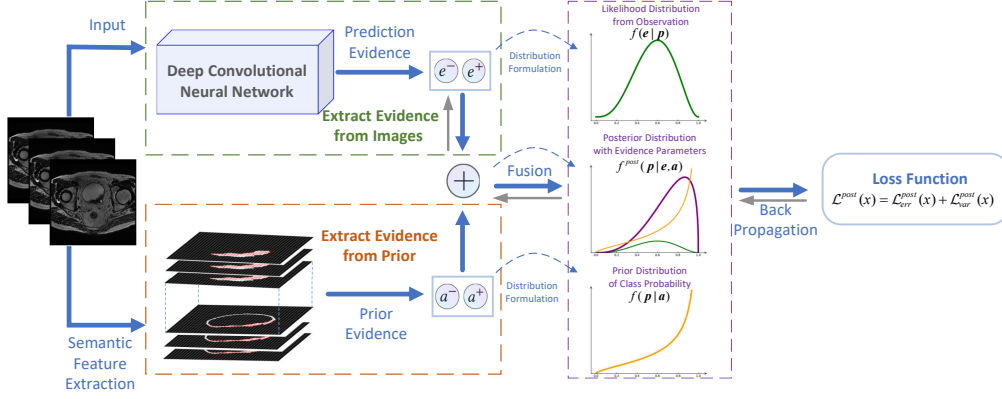


Figure 1: Workflow of PENet.

169 determine the stage of bladder tumors, based on clinical experiences. There-
 170 fore, high tumor-bladder wall overlap suggests high cancer stage ($\geq T2$),
 171 whereas little overlap indicates low stage ($< T2$). Since tumor and blad-
 172 der wall segmentation masks are used in clinical previous staging of bladder
 173 cancer, we determined the degree of overlap

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

174 assuming that M_{tumor} and M_{wall} refer to the MR image-derived tumor and
 175 bladder wall mask matrices, respectively, $\langle \cdot, \cdot \rangle$ represents the Frobenius inner
 176 product of the two. Obtain ϱ_i by further normalizing the overlap degree ρ_i
 177 for each picture i , such as $\rho_i = \frac{\varrho_i - \varrho^{min}}{\varrho^{max} - \varrho^{min}}$.

178 Using two instances, shown in Figure 2, we can better understand how
 179 much overlap there is between tumors and the bladder wall and how advanced
 180 the disease is. When ρ rises, so does the stage of bladder cancer, which may
 181 range anywhere from $< T2$ to $\geq T2$. In the following part, we used ρ to
 182 create prior evidence to fuse into PENet for bladder cancer stage.

183 3.3. PENet to classify bladder cancer stage

184 The deep neural network can be understood as stacking several non-linear
 185 function with a softmax operator on top to discriminate the training data,
 186 which is parameter regression framework of Multinomial distribution. Cur-
 187 rently, we are all aware that the traditional deep neural network is overconfi-
 188 dent since the denominator of softmax has squished the output probabilities,

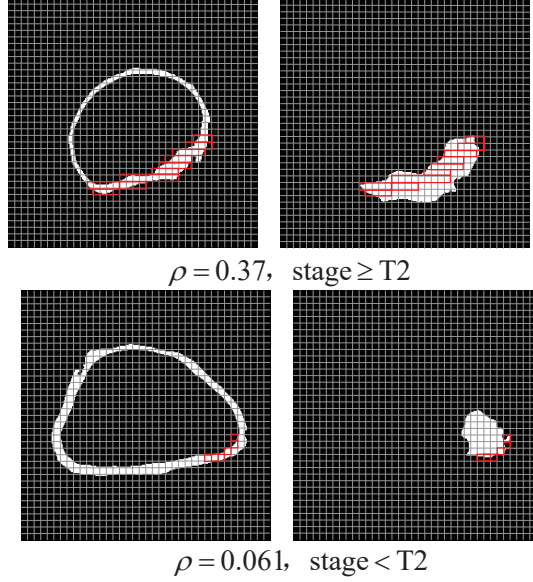


Figure 2: Calculating prior evidences from segmentation of bladder tumor and wall.

189 and the point estimation of class probability which is first-order uncertainty
190 can be proceed by the cross entropy loss function but cannot express the
191 variance of prediction probability such as second-order uncertainty. As men-
192 tioned in Section 2.2, evidential deep neural network (EvidentialNet)[34] pro-
193 poses a principled way to formulate the prediction probability distribution
194 with evidence parameter which can directly express the variance of predic-
195 tion and accomplish reliable classification. In contrast to EvidentialNet, we
196 consider the fact that the class probability’s prior distribution should not
197 be disregarded when class probability is seen as a random variable. More-
198 over, we can directly infer the expression of the posterior distribution of the
199 class probability through the distribution assumption and Bayesian Theorem.
200 Through the loss function reconstructed by the posterior distribution, PENet
201 can provide more stable and accurate prediction to improve performance.

In this paragraph, we will carefully derive the expression for the poste-
rior distribution of class probability. First, according to the observations of
the DCNN, we assume that the likelihood function is a *Binomial* distribu-
tion $f(\mathbf{e} \mid \mathbf{p}) = C_{e^+ + e^-}^{e^+} p_0^{e^-} p_1^{e^+}$, where distribution parameter $\mathbf{e} = (e^-, e^+)$
is extracted evidence from DCNN to support stage $< T2$ and stage $\geq T2$
respectively, and $\mathbf{p} = (p_0, p_1)$ is class probability. Second, on the basis of the

conjugate prior distributions, we assume that the prior distribution about class probability is a *Beta* distribution $f(\mathbf{p} \mid \mathbf{a}) = \text{Beta}(\mathbf{p} \mid 2a^-, 2a^+) = \frac{1}{B(2a^-, 2a^+)} p_0^{2a^- - 1} p_1^{2a^+ - 1}$, where $\mathbf{a} = (a^-, a^+)$ is the prior evidence of tumor infiltration that support stage $< \text{T2}$ and stage $\geq \text{T2}$ respectively. This prior distribution function satisfies that when there is no prior knowledge for classification $a^- = a^+ = 0.5$, we have $\text{Beta}(\mathbf{p} \mid 2a^-, 2a^+) = 1$, which is a uniform distribution. So we can directly conclude that the posterior distribution $f^{post}(\mathbf{p} \mid \mathbf{e}, \mathbf{a})$ is also a *Beta* distribution. According to Bayesian theorem, we can directly calculate the specific expression of the posterior probability distribution as

$$\begin{aligned}
f^{post}(\mathbf{p} \mid \mathbf{e}, \mathbf{a}) &= \frac{f(\mathbf{p} \mid \mathbf{a}) * f(\mathbf{e} \mid \mathbf{p})}{\int_0^1 f(\mathbf{p} \mid \mathbf{a}) * f(\mathbf{e} \mid \mathbf{p}) d\mathbf{p}}, \\
&= \frac{C_{e^+ + e^-}^{e^+} p_0^{e^-} p_1^{e^+} * \frac{1}{B(2a^-, 2a^+)} p_0^{2a^- - 1} p_1^{2a^+ - 1}}{\int_0^1 C_{e^+ + e^-}^{e^+} p_0^{e^-} p_1^{e^+} * \frac{1}{B(2a^-, 2a^+)} p_0^{2a^- - 1} p_1^{2a^+ - 1} d\mathbf{p}}, \\
&= \frac{p_0^{e^- + 2a^- - 1} p_1^{e^+ + 2a^+ - 1}}{\int_0^1 p_0^{e^- + 2a^- - 1} p_1^{e^+ + 2a^+ - 1} d\mathbf{p}}, \\
&= \frac{p_0^{e^- + 2a^- - 1} p_1^{e^+ + 2a^+ - 1}}{\mathcal{B}(e^- + 2a^-, e^+ + 2a^+)}, \\
&= \text{Beta}(e^- + 2a^-, e^+ + 2a^+), \tag{2}
\end{aligned}$$

where $\mathcal{B}(\cdot)$ is *Beta* function. We are able to construct the prior evidences a_i^-, a_i^+ for each samples i as the parameters of f^{post} by

$$a_i^- = 1 - \rho_i, \quad a_i^+ = \rho_i. \tag{3}$$

202 which is based on the value of ρ_i that was acquired by quantifying the clinical
203 prior in Section 3.2 for each sample.

Given $\mathcal{D} = \{x_i, \mathbf{y}_i\}_{i=1}^N$ of N labeled MR images, is subject to the following declarations: one-hot label vector x_i , $\mathbf{y}_i = (0, 1)$ when stage $\geq \text{T2}$, and $\mathbf{y}_i = (1, 0)$ when stage $< \text{T2}$, are represented by $\mathbf{y}_i = (y_{i0}, y_{i1})$. We are able to define the loss function as the expectation of mean squares error $\|\mathbf{y}_i - \mathbf{p}_i\|_2^2$ on the basis of $f^{post}(\mathbf{p} \mid \mathbf{e}, \mathbf{a})$. The loss function of PENet is

denoted as $\sum_{i=1}^N \mathcal{L}^{post}(x_i)$, for each sample x_i the loss is

$$\begin{aligned}
\mathcal{L}^{post}(x_i) &= \int \|\mathbf{y}_i - \mathbf{p}_i\|_2^2 f^{post}(\mathbf{p}_i \mid \mathbf{e}_i, \mathbf{a}_i) d\mathbf{p}_i \\
&= E_{f^{post}} [\|\mathbf{y}_i - \mathbf{p}_i\|_2^2] \\
&= \sum_{j=0}^1 E_{f^{post}} [y_{ij}^2 - 2y_{ij}p_{ij} + p_{ij}^2] \\
&= \sum_{j=0}^1 (y_{ij}^2 - 2y_{ij}E_{f^{post}}(p_{ij}) + E_{f^{post}}(p_{ij}^2)). \tag{4}
\end{aligned}$$

Due to $E_{f^{post}}(p_{ij}^2) = E_{f^{post}}(p_{ij})^2 + Var_{f^{post}}(p_{ij})$, we are able to deduce the equation and arrive at

$$\begin{aligned}
\mathcal{L}^{post}(x_i) &= \sum_{j=0}^1 (y_{ij} - E_{f^{post}}(p_{ij}))^2 + Var_{f^{post}}(p_{ij}) \\
&= \underbrace{\left(y_{i0} - \frac{e_i^- + 2a_i^-}{\mathcal{S}_i}\right)^2 + \left(y_{i1} - \frac{e_i^+ + 2a_i^+}{\mathcal{S}_i}\right)^2}_{\mathcal{L}_{err}^{post}} \\
&\quad + \underbrace{\frac{2(e_i^- + 2a_i^-)(e_i^+ + 2a_i^+)}{\mathcal{S}_i^2(\mathcal{S}_i + 1)}}_{\mathcal{L}_{var}^{post}}, \tag{5}
\end{aligned}$$

204 where $\mathcal{S}_i = e_i^- + e_i^+ + 2$. Because of this novel loss function, we are able to
205 evaluate whether or not we can improve the performance for bladder cancer
206 stage. We can deduce from Equation (5) that the loss function of PENet is
207 made up of two components: the prediction error term \mathcal{L}_{err}^{post} and the predic-
208 tion variance term \mathcal{L}_{var}^{post} respectively. This indicates that we may reduce the
209 prediction error as well as the variance in the data at the same time by reduc-
210 ing the loss function concurrently. In addition, we make the assumption that
211 the prediction error and variance are denoted by the symbols \mathcal{L}_{err} and \mathcal{L}_{var} ,
212 respectively, when class probability prior distribution is a uniform distribu-
213 tion. Through the application of the following two theorems, we conduct an
214 investigation into how the accuracy of the prediction may be improved by
215 posterior distribution of class probability with evidence parameters.

216 **Theorem 1.** When $a^- < a^+$ in a negative case or $a^+ > a^-$ in a positive
 217 case, we have $\mathcal{L}_{err} > \mathcal{L}_{err}^{post}$.

proof: The prediction error term \mathcal{L}_{err} of EvidentialNet may be obtained as follows with uniform prior distribution

$$\mathcal{L}_{err} = \left(y_0 - \frac{e^- + 1}{\mathcal{S}}\right)^2 + \left(y_1 - \frac{e^+ + 1}{\mathcal{S}}\right)^2. \quad (6)$$

On the other hand, predictive error terms given by posterior distribution is

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

Due to the fact that $a^+ > a^-$, $a^+ + a^- = 1$, we may deduce that $e^- + 2a^- < e^- + 1$ and $e^+ + 2a^+ > e^+ + 1$ respectively. Further inference may be drawn from the fact that (6) and (7) both indicate

$$\begin{aligned} \left(y_0 - \frac{e^- + 1}{\mathcal{S}}\right)^2 &> \left(y_0 - \frac{e^- + 2a^-}{\mathcal{S}}\right)^2, \\ \left(y_1 - \frac{e^+ + 1}{\mathcal{S}}\right)^2 &> \left(y_1 - \frac{e^+ + 2a^+}{\mathcal{S}}\right)^2, \\ \mathcal{L}_{err} &> \mathcal{L}_{err}^{post}. \end{aligned} \quad (8)$$

218 The procedure for providing evidence for negative cases is the same as de-
 219 scribed previously.

220 **Theorem 2.** We have $\mathcal{L}_{var} > \mathcal{L}_{var}^{post}$ if $(e^+ - e^-)(a^+ - a^-) > 0$ in each and
 221 every case.

proof: The prediction variance term \mathcal{L}_{var} of EvidentialNet may be obtained as follows with uniform prior distribution

$$\mathcal{L}_{var} = \frac{2(e^- + 1)(e^+ + 1)}{\mathcal{S}^2(\mathcal{S} + 1)}. \quad (9)$$

We have shown that the prediction variance term fused prior distribution \mathcal{L}_{var}^{post} in (5) gets the following results:

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

As a result that $(1 - 4a^+a^-) \geq 0$ and $a^+ + a^- = 1$, we obtain

$$\mathcal{L}_{var} - \mathcal{L}_{var}^{post} = \frac{(e^+ - e^-)(a^+ - a^-) + (1 - 4a^+a^-)}{\mathcal{S}^2(\mathcal{S} + 1)} > 0. \quad (10)$$

222 With the help of Theorem 1’s derivation proof, we can create an ap-
 223 proach for figuring out whether or not prior evidence may be incorporated
 224 into PENet and so selecting out evidence that could increase prediction error.
 225 When the prior evidence is consistent with the ground truth, the posterior
 226 distribution calculated by the integrated prior distribution can reduce the
 227 prediction error of PENet. Regarding Theorem 2, we are aware that if the
 228 evidences of the classification and the prior evidences are consistent, PENet
 229 can provide lower prediction variance by a sharp posterior distribution of
 230 class probability. It is our goal to use the Bayesian theory to create the *Beta*
 231 posterior distribution of class probability with two sources evidence param-
 232 eters and reformulate the objective function as the expectation of prediction
 233 error, which may be reduced by the derivation proofs of the prediction er-
 234 ror and variance. Algorithm 1 provides a summary of the process of model
 235 training.

Algorithm 1 Workflow of model training

1. Calculate prior evidence \mathbf{a} from segmentation of bladder tumor and wall according to (1) and (4);
 2. Generate prediction evidence \mathbf{e} from images through deep neural network;
 3. According to (3), compute posterior distribution of class probability and obtain $\mathcal{L}^{post}(x_i)$ for each images;
 4. Optimize the PENet by decreasing \mathcal{L}_{err}^{post} and \mathcal{L}_{var}^{post} until convergence.
-

236 4. Experiment Results

237 During the course of the experiments, we gather the MR images of pa-
 238 tients with bladder cancer for stage prediction from two distinct parts: our
 239 cooperation hospital and the Chinese University Computer Design Compe-
 240 tition. The dimension of each MR image is 512 pixels on 512 pixels, and
 241 the image data collection comprises 344 T2-weighted MR images of 38 indi-
 242 viduals. High stage to low stage ratio is 1.26 to 1, and all MR images have

243 been identified as MIBC (stage $\geq T2$) or NMIBC by human clinicians (stage
244 $<T2$).

245 In order to apply classification algorithms to MR images and accurately
246 forecast the cancer stage (high or low), we divided the data set by patients
247 and carried out five-fold cross validation in order to put our experiments into
248 action. Metrics such as *accuracy*, *precision*, *recall rate* and *F1-score* are also
249 used to assess the effectiveness of image classification techniques. In all, there
250 are two parts to the experiments. The first part of the analysis will determine
251 whether the planned PENet is successful in predicting the stage of bladder
252 cancer. PENet’s superiority over other representative picture classification
253 algorithms will be tested in the second part.

254 4.1. Increasing efficiency of predictions by prior integration

255 Ablation experiments are used in this part to verify the prediction im-
256 provement obtained by incorporating clinical prior evidence into DCNN. In
257 order to stage bladder cancer, we make use of three different deep convolu-
258 tional neural networks, namely ResNet[38], EvidentialNet[34], and PENet.
259 ResNet18’s backbone network model [38] is used in all of the DCNNs men-
260 tioned. Table 1 provides an overview of the classification performance. When
261 we compare ResNet with EvidentialNet, we discover that evidence theory’s
262 capacity to turn prediction probabilities into distributions of prediction prob-
263 abilities leads to performance improvements. All of the assessment metrics of
264 accuracy, precision, recall rate, and F1–score are further raised by +8.91%,
265 +11.44%, +4.96%, and +8.35% respectively when the stable posterior dis-
266 tribution is obtained by PENet by superimposing prior evidences to Eviden-
267 tialNet. PENet’s increased capacity to stage bladder cancer was shown by
268 this experiment, which indicated that prior evidence integration improved
269 the prediction of the disease.

Table 1: Ablation studies of integrating prior evidences

	ResNet	EvidentialNet	PENet	Improvement
<i>Accuracy</i>	72.14	83.86	92.77	+8.91%
<i>Precision</i>	70.43	80.40	91.84	+11.44%
<i>Recall</i>	84.19	90.05	95.01	+4.96%
<i>F1-score</i>	76.06	84.84	93.19	+8.35%

270 Next, some hard-to-classified cases which are shown in Figure 3 are pro-
271 vided to verify the performance improvement of PENet over EvidentialNet
272 due to integrating prior distribution with prior evidence parameter and we
273 will analyze it from three aspects.

274 The first aspect is that PENet can rectify samples that are misclassified by
275 EvidentialNet, as shown in the first four cases in Figure 3. For low stage, The
276 shape and intensity of the shaded region within the red circle correspond
277 to bladder tumors which is why EvidentialNet produced inaccurate stage
278 $\geq T2$ forecasts. The correct classification was accomplished in Figure 3(a) by
279 integrating the evidence of non-tumor-infiltration into PENet to enhance the
280 prediction probability to 0.86. In a similar way, PENet was able to enhance
281 the low-stage predictions given by EvidentialNet at $p_0 = 0.24$ to $p_0 = 0.77$
282 for proper classification in Figure 3(c). This is the result of making the class
283 probability posterior distribution closer to the true distribution by learning
284 the prior evidence from the segmentation mask.

285 For high stage, EvidentialNet may come to the wrong conclusion about
286 the stage of the cancer if the intensity of the tumor is comparable to the
287 bladder wall. In Figure 3(b) and (d), the quantified previous evidences of
288 tumor-infiltration made it possible for PENet to enhance the predictions
289 given by EvidentialNet from $p_1 = 0.35$ and $p_1 = 0.50$ to $p_1 = 0.93$ and
290 $p_1 = 0.76$, respectively.

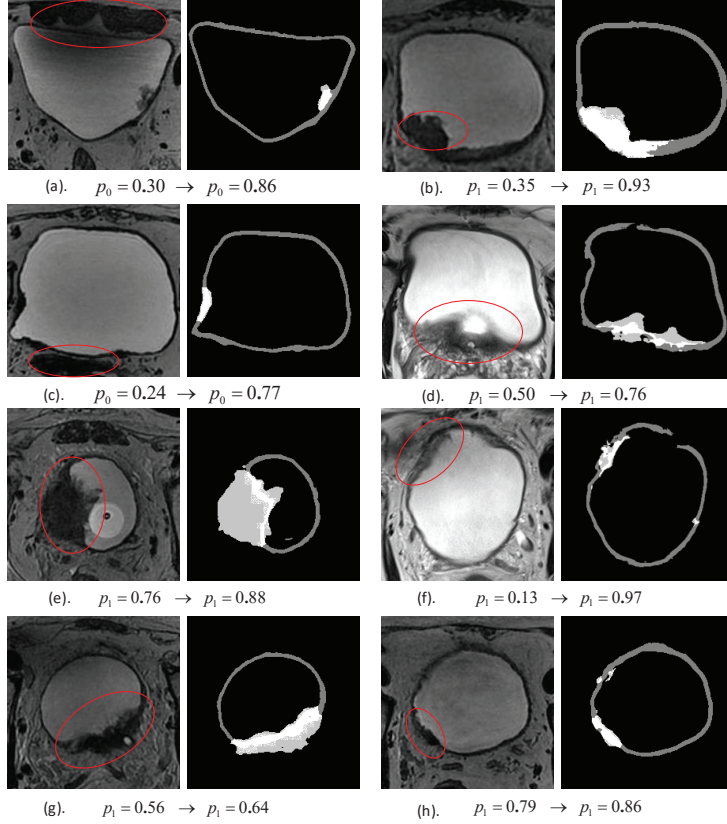


Figure 3: Cases of cancer stage prediction improvements brought by prior evidences.

291 The second aspect is that fusing prior evidences into PENet can enhance
 292 the confidence of correct prediction produced by EvidentialNet. In Figure
 293 3(e), PENet improves the prediction of EvidentialNet from $p_1 = 0.76$ to
 294 $p_1 = 0.88$, which improves the confidence of the prediction due to prior
 295 evidences. Figure 3(g) provides a case of a low confidence prediction for
 296 EvidentialNet. PENet improves confidence by boosting prediction from $p_1 =$
 297 0.56 to $p_1 = 0.64$.

298 The third aspect is that the prior evidences can help PENet to deal with
 299 the confusing cases. Figure 3(f) and (h) present two cases that are very
 300 challenging for EvidentialNet to correctly identify the tumor stage. Eviden-
 301 tialNet fails to recognize the existence of the tumor in Figure 3(f) because
 302 the tumor is so intimately linked to the wall of the bladder. As a result, the
 303 EvidentialNet generates an incorrect prediction of $p_1 = 0.13$. On the other

hand, in our approach, precise prior evidence parameter directs PENet to generate the correct prediction of high cancer stage $p_1 = 0.97$. The tumor’s attachment to the bladder wall is quite thin in Figure 3(h). EvidentialNet, while its proper classification, may not concentrate on the lesion’s precise location. According to the PENet’s improved prediction of $p_1 = 0.86$, a more advanced stage of cancer was confirmed.

Extracting clinical prior evidence to get reliable posterior distribution of class probability for PENet provides more effective correction of misclassifications, increased confidence in prediction, and improved capacity to handle the hard instances. Because of this, PENet is a promising tool for integrating clinical evidence to improve performance and interpretation.

4.2. Compared to different bladder cancer staging methods

We tested PENet’s performance against that of four other DCNN-based image classification techniques such as ResNet18[38], DenseNet[39], EvidentialNet[34], and a rule-integrated approach such as RuleNet[25]. We discovered that PENet’s performance was superior to each of these other methods. In Figure 4 and Table 2, the evaluation metrics generated by the five different approaches are shown, while Table 3 displays the more refined findings of the five-fold cross-validation.

Table 2: Comparison of different cancer stage classification 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>PENet</i>	92.77	91.84	95.01	93.19

Because integrating prior evidence parameter makes PENet’s prediction of the cancer stage more accurate and trustworthy, we may find that PENet improves all assessment metrics in comparison to other methods. Because integrating prior evidences helps PENet better predict the cancer stage with reliable posterior distribution. RuleNet and PENet, both of which are directed by clinical rules and prior evidences, outperform solely data-driven DCNN models such as ResNet, DenseNet, and EvidentialNet, as can be shown in the Figure 4. On the other hand, RuleNet takes a lot of data for

Table 3: Cross validation results of cancer stage classification methods.

Cross Validation 1	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	85.06	82.19	100.0	90.23
<i>DenseNet</i>	85.06	87.30	91.67	89.43
<i>EvidentialNet</i>	89.66	86.96	100.0	93.02
<i>RuleNet</i>	82.76	80	100.0	88.88
<i>Our Method</i>	93.10	93.55	96.67	95.08
Cross Validation 2	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	84.13	85.19	79.31	82.14
<i>DenseNet</i>	77.78	72.73	82.76	77.42
<i>EvidentialNet</i>	84.13	82.76	82.76	82.76
<i>RuleNet</i>	88.88	90.24	85.86	88.00
<i>Our Method</i>	90.48	96.00	82.76	88.89
Cross Validation 3	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	69.12	69.44	71.43	70.42
<i>DenseNet</i>	80.88	72.92	100.0	84.34
<i>EvidentialNet</i>	83.82	81.58	88.57	84.93
<i>RuleNet</i>	83.82	77.27	97.14	86.07
<i>PENet</i>	92.65	87.50	100.0	93.33
Cross Validation 4	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	61.36	53.57	78.95	63.83
<i>DenseNet</i>	75.00	68.18	78.95	73.17
<i>EvidentialNet</i>	77.27	71.43	78.95	75.00
<i>RuleNet</i>	86.36	88.23	78.94	83.33
<i>PENet</i>	95.45	90.48	100.0	95.00
Cross Validation 5	Accuracy	Precision	Recall	F1 score
<i>ResNet</i>	61.04	61.76	91.3	73.68
<i>DenseNet</i>	75.32	77.55	82.61	80.00
<i>EvidentialNet</i>	84.42	79.43	100.0	88.46
<i>RuleNet</i>	84.41	82.69	93.47	87.75
<i>PENet</i>	92.21	91.67	95.65	93.62

331 an additional network to acquire clinical decision rules, whereas PENet per-
 332 forms better on a less amount of training data. In addition, prior evidences
 333 are chosen in accordance with Theorems 1 and 2 to guarantee that the in-
 334 tegrated prior evidences will minimize prediction error and variance, which
 335 ultimately leads to more accurate and stable predictions.

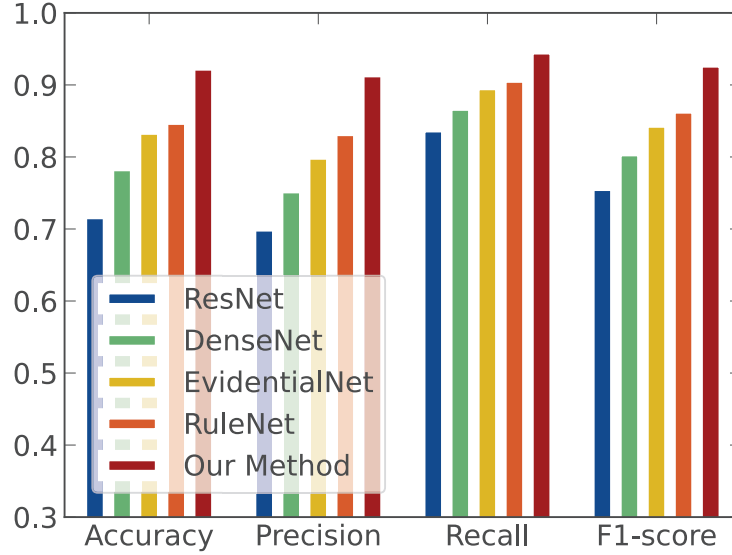


Figure 4: Comparison of different cancer stage classification methods.

336 Last, the regions of interest (ROI) in MR images that were created by five
 337 different classification methods were shown in an intelligible way by Grad-
 338 CAM[40]. Each of the ROI visualizations that have been developed is shown
 339 in the Figure 5.

340 It has been observed that the distribution of ROIs produced by ResNet
 341 and DenseNet in MR images is unstable and that it comprises numerous areas
 342 that are unrelated to bladder cancers. Possible causes include the fact that
 343 the limited labeled MR images do not guarantee that ResNet and DenseNet
 344 concentrate on the lesion region where the tumor is situated and that they
 345 might be impacted by areas that are not associated. In contrast to these
 346 two methods, EvidentialNet may partly relieve the data shortages by utiliz-
 347 ing evidence to formalize the prediction distribution in order to accomplish
 348 classification. According to EvidentialNet’s prediction performance, it is not
 349 steady even though the shapes and intensity of the areas are similar to blad-
 350 der tumor. Clinical experience rules included into RuleNet provide more

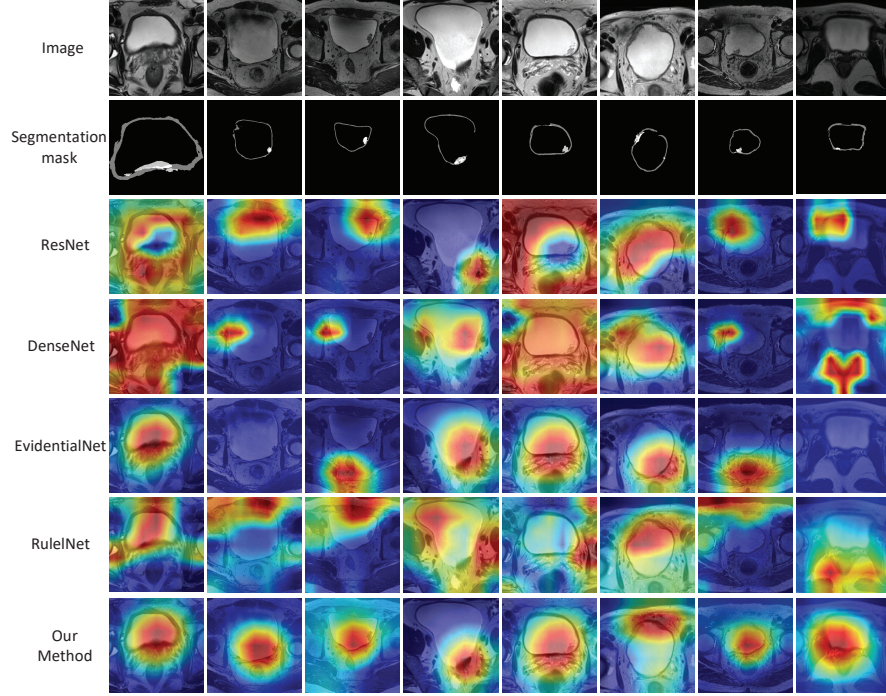


Figure 5: Visualization of ROIs in MR images produced by comparative classification methods.

351 accurate and stable ROIs than data-driven DCNNs but they are sensitive in
 352 the background noise area. With the help of incorporating prior evidences
 353 from clinical experiences that are extracted from the tumor-wall segmenta-
 354 tion masks to get reliable posterior distribution, PENet’s ROIs focus on the
 355 overlap regions between the bladder tumor and the wall stably and robustly.
 356 In conclusion, as shown by the outcomes of ROI visualization, the capacity
 357 of PENet to make precise predictions about the stage of cancer is beneficial
 358 from its capacity to integrate knowledge gained from clinical experiences.

359 5. Conclusion

360 It is possible that deep neural networks cannot accurately anticipate the
 361 bladder cancer stage at which cancer will be found due to a lack of relevant
 362 clinical expertise. We offer a strategy that is effective and for generating
 363 prior evidences of tumor-infiltration in order to quantify clinical experiences.
 364 Following that, we fused prior evidences as posterior distribution parameter

of class probability into PENet in order to increase the accuracy of cancer stage prediction. Experiments have shown that PENet is beneficial for identifying the stage of bladder cancer. In future research, a lot of focus will be taken at the gap that may be seen between the predictions offered by neural networks and the clinical knowledge that has already been gathered.

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