Comparative Analyses of Attention-Based Multiple Instance Learning Methods for Bladder Cancer Pathologic T-Category Classification

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BACKGROUND

- **Determining pathological T (pT) category in invasive urothelial carcinoma from transurethral resection of bladder (TURB) specimens** is challenging due to tissue fragmentation and artifacts, and its study for deep-learning based approach has been less studied than radial cystectomy samples.
- Deep learning (DL) based applications for pathology diagnosis typically require burdensome manual annotations, and **multiple instance learning (MIL)** has been widely used in pathology, with many variations improving its performance.
- We tried to use MIL-based approach to not only discern carcinoma, but categorize pT category by implementing MIL-based techniques, and implemented modifying some of the proposed techniques in the literature.

Related Works

- **Attention-based Deep Multiple Instance Learning (Ilse et al., 2018):**
  - Neural network-based attention mechanism for MIL that provides insight into each instance's contribution to bag classification.
  - Outperformed other methods on histopathology datasets while maintaining interpretability with learnable attention mechanism.
- **Clinical-grade Computational Pathology (Campanella et al., 2019):**
  - A weakly supervised DL system with fixed top-K instance selection validated on 44,732 WSIs from 15,187 patients.
  - Achieved AUCs above 0.98 for prostate cancer, basal cell carcinoma, and breast cancer metastases detection.
- **Joint Breast Neoplasm Detection and Subtyping (Casson, Liu et al., 2023):**
  - A multi-resolution network using top-K MIL with adaptive K selection via Otsu's thresholding method on over 125,000 WSIs.
  - Utilized transformer architecture to integrate features across magnification levels for comprehensive breast neoplasm analysis.

METHODS

- **Patient data selection and experimental setup**
  - Analyzed 5,673 matched H&E-stained megapatches from bladder cancer TURB whole slide image (WSI) specimens from 55 patients (mean images per patient: 56.73; min: 7; max: 175), scanned with PANNORAMIC™ Digital Slide Scanner (3DHISTECH)
  - Used megapatches (1024 × 1024 pixels) instead of whole slide images for computational efficiency
  - Dataset distribution: T1 (2978 patches, 52.5%), T2 (2695 patches, 47.5%)
  - Experiments conducted on NVIDIA A100 80GB GPU with CUDA 11.3
- **Model architecture**

1. **Bi-Resolution Top K-MIL Approach (Figures 1&2)**
   - Processed megapatches at dual magnifications (400x and 50x) separately
   - Used SEResNet18 for feature extraction with adaptive Top-K patch selection
   - Employed Otsu thresholding to automatically determine optimal K value
   - Integrated features with transformer architecture to combine information across magnifications

2. **Weighted Attention MIL (Figures 1&2)**
   - CNN backbone at 200x magnification with fully convolutional network layers
   - FCN with attention layer with automatic feature weighting

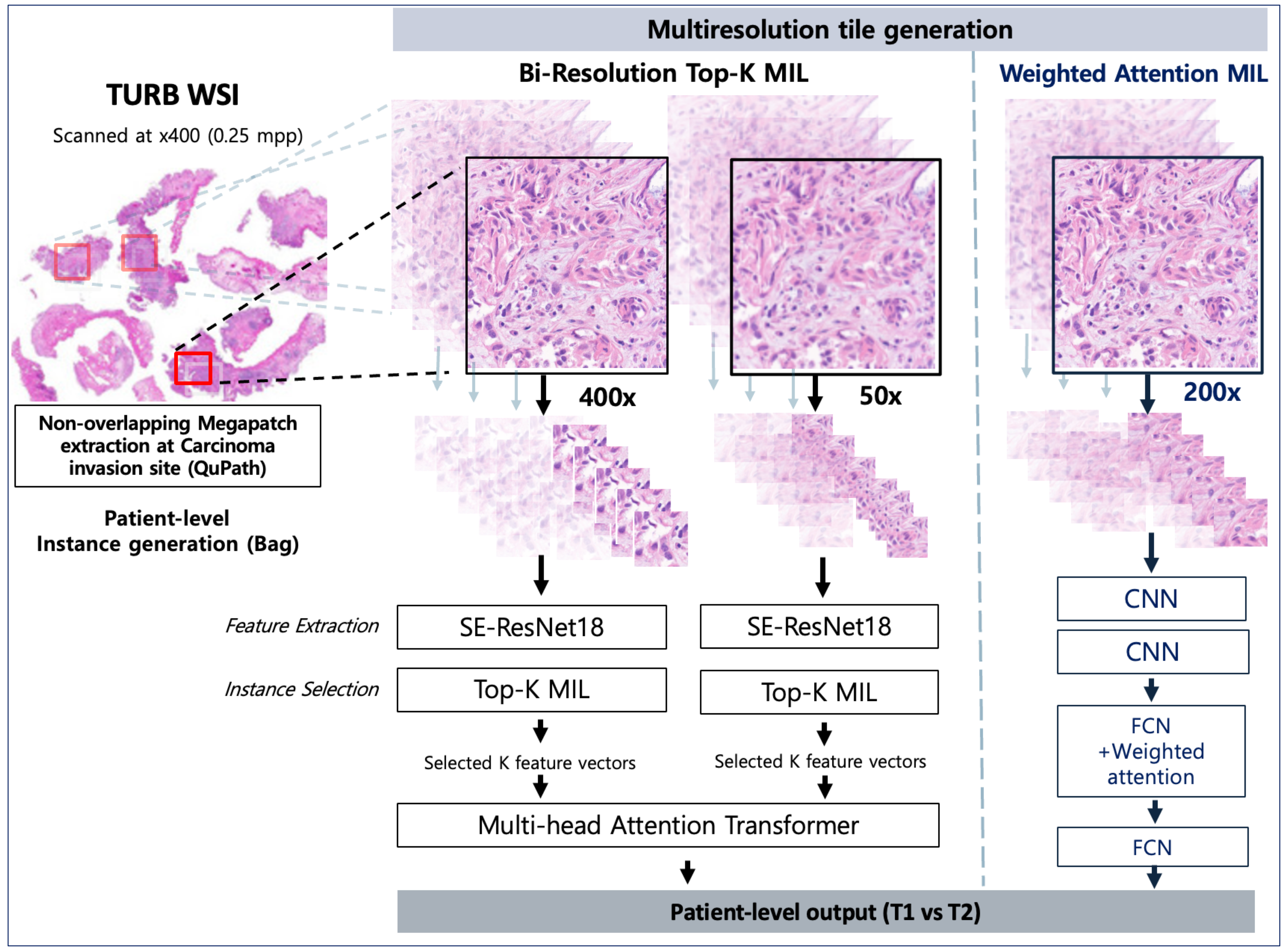
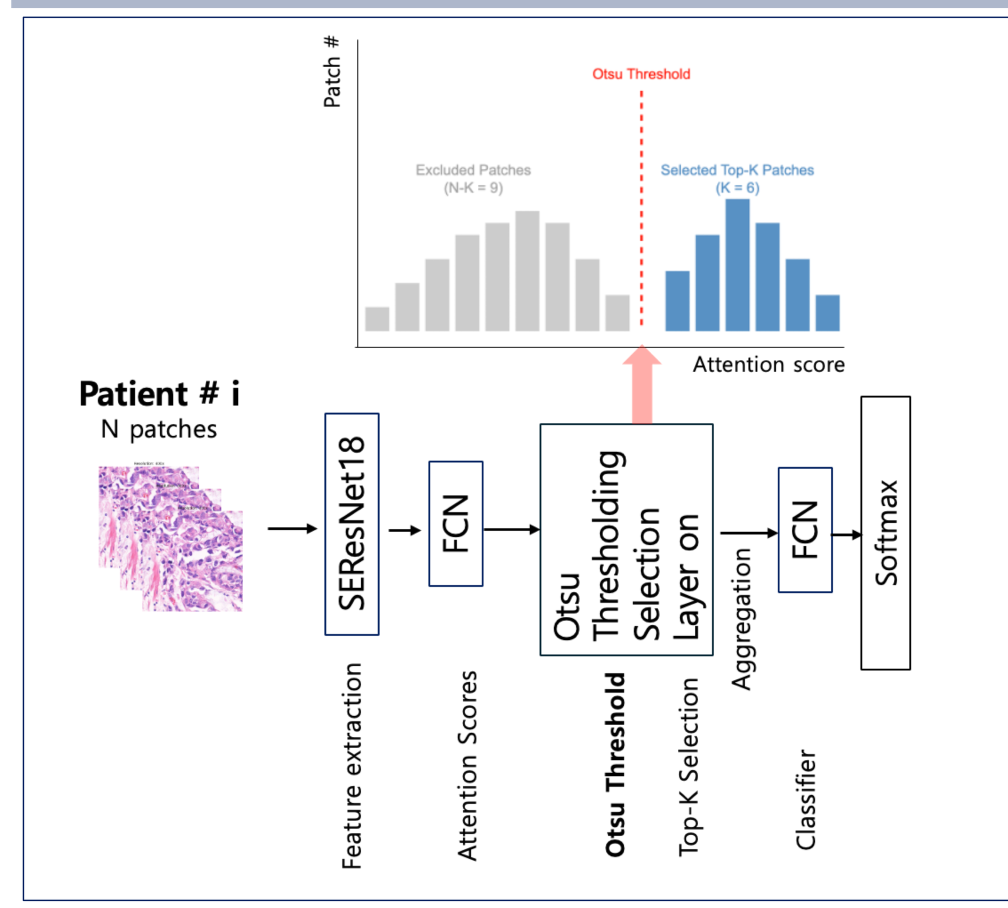
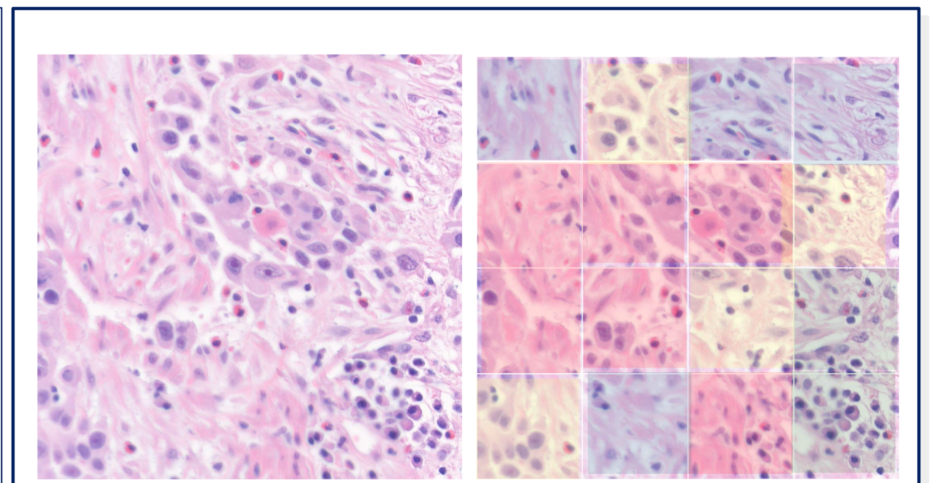


Figure 1. Schematic View of the Comparative MIL approaches for pathological tumor staging using multiresolution Megapatches. *WSI, Whole Slide Image; TURB, Transurethral Resection of Bladder; mpp, microns per pixel; MIL, Multiple Instance Learning; CNN, Convolutional Neural Network; FCN, Fully Connected Network; SE-ResNet18, Squeeze-and-Excitation ResNet (18 layers); QuPath, Open-source software for digital pathology analysis.*





- High attention weight (0.8-1.0) - Critical diagnostic regions showing invasion into muscle layer (T2 indicator)
- Medium-high attention weight (0.6-0.8) - Regions containing suspicious cellular patterns
- Medium attention weight (0.4-0.6) - Regions with abnormal cells but unclear invasiveness
- Low-medium attention weight (0.2-0.4) - Regions with some abnormal features
- Low attention weight (0.0-0.2) - Non-informative or normal tissue regions

Figure 2. Illustration of the Top K MIL algorithm & Attention-based MIL Representation

RESULTS

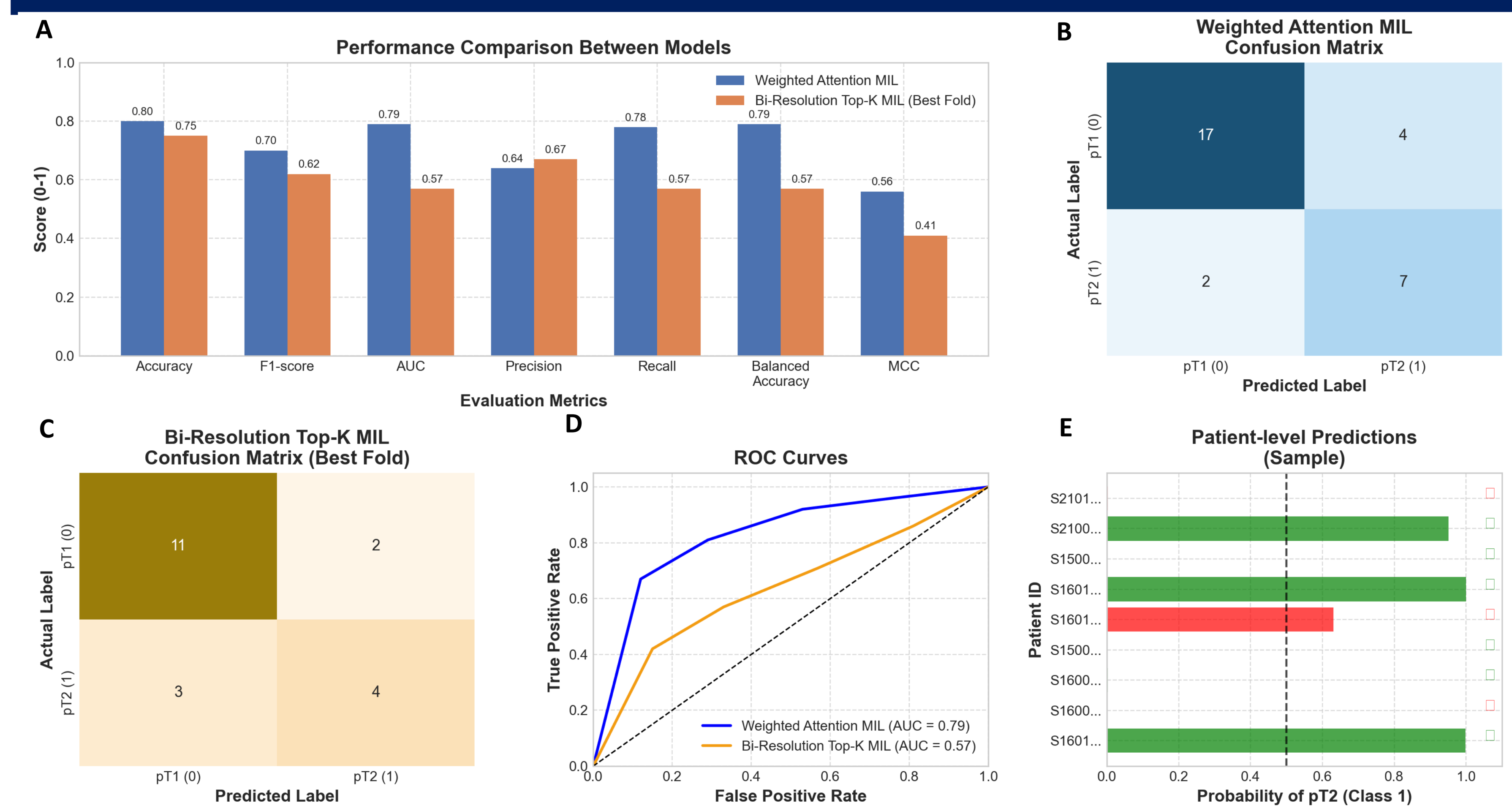


Figure 3. Performance evaluation of bladder cancer staging classification models. (A) Comparative performance metrics between Weighted Attention MIL and Bi-Resolution Top-K MIL (best fold) approaches. **(B)** Confusion matrix of Weighted Attention MIL showing the distribution of predictions across actual pT1 and pT2 classes. **(C)** Confusion matrix of Bi-Resolution Top-K MIL (best fold) demonstrating prediction distribution. **(D)** ROC curves for both models showing discriminative capability with AUC of 0.79 for Weighted Attention MIL and 0.57 for Bi-Resolution Top-K MIL. **(E)** Patient-level prediction probabilities for selected cases, with green bars indicating correct predictions and red bars indicating misclassifications (dashed line represents the classification threshold at 0.50).

DISCUSSION AND CONCLUSION

- Our approach demonstrates effectiveness beyond simple cancer vs. normal classification, successfully distinguishing between T1 and T2 staging.
- Tile-level processing offers computational efficiency while maintaining discriminative power, avoiding the extensive GPU resources and background processing required for full WSI analysis.
- Rescaled images don't provide the same advantages as true multi-scanning approaches due to missing contextual information: Low-resolution scaled images may potentially confuse rather than enhance the model.
- Findings suggest selective attention to discriminative regions may be more valuable, particularly when working with limited training datasets.

CONTACTS

- Data and code availability: Please e-mail us. We are happy to provide details!
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