Clinical Research Program

Project name: Prospective Validation of Pathology-based Artificial Intelligence Diagnostic Model for Lymph Node Metastasis in Prostate Cancer

Bidding organization: Sun Yat-sen Memorial Hospital

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I. Summary of the research program

Lymph node metastasis is a prevalent mode of spread in prostate cancer, and accurate postoperative pathological lymph node staging holds significant implications for subsequent treatment and prognosis. However, the existing approach to pathological assessment relies on manual image review by pathologists, leading to low diagnostic efficiency and potential missing diagnosis of micrometastases. In our prior study, we addressed this challenge by developing a deep learning-based AI diagnostic model (named ProCaLNMD) for prostate cancer lymph node metastasis detection. The model demonstrated promising results in retrospective validation.

This study, framed as a diagnostic trial without intervention, seeks to enroll patients who have undergone radical prostatectomy with pelvic lymph node dissection for prostate cancer, possessing comprehensive clinical and pathologic data. The study is planned to enroll approximately 200 patients in our center, with 2,000 images of corresponding pathological lymph node sections from these patients, and gather the relevant clinicopathological data to prospectively validate the performance of the AI model.

II. Background of the study

Globally, prostate cancer ranks as the second most common malignant tumor in men, surpassed only by lung cancer. It stands out as the predominant malignant tumor within the male genitourinary system and holds the highest incidence in the male urogenital system[1]. Lymph node metastasis serves as a prevalent way of its spread, and the identification of regional lymph node metastasis plays a pivotal role in guiding subsequent postoperative treatment and determining prognosis. Despite its significance, achieving accurate pathologic lymph node staging remains a formidable challenge, particularly when dealing with micrometastases. The inherent characteristics of these

lesions, such as small diameters, minimal lesion involvement, and the limited resolution of the human eye, can contribute to missing diagnoses. Conventional pathology has demonstrated restricted sensitivity in detecting micrometastases, posing an increased risk of cancer progression and potential delays in implementing adjuvant therapy. While immunohistochemistry and molecular markers can enhance the detection of micrometastases, they are expensive and not routinely used[2].

In recent years, the widespread adoption of artificial intelligence in digital pathology diagnosis has been facilitated by advancements in whole slide imaging technology, coupled with increased computational power and data storage capacity[3]. This technology has the capability to extract image features from pathological images that may be missed by the human eye, enabling accurate disease diagnosis, prognosis assessment, and treatment predictions. Literature reports highlight the successful construction of a deep learning-based AI diagnostic model for lymph node metastasis in breast cancer. The diagnostic performance of this model has been shown to rival that of experts[4]. Our previous study involved the development and retrospective validation of a deep learning-based AI diagnostic model for pathological lymph node staging in prostate cancer. This model utilized postoperative resected lymph node pathological images, complemented by the construction of AI-assisted software for pathological lymph node reading. In retrospective validation, the AI system demonstrated strong performance, with diagnostic sensitivity comparable to senior pathologists. This capability holds promise in assisting physicians by reducing missed diagnoses of micrometastases and enhancing diagnostic accuracy and efficiency. However, there remains a need for a well-established prospective validation to assess the diagnostic proficiency and practical application of this model in a real clinical setting.

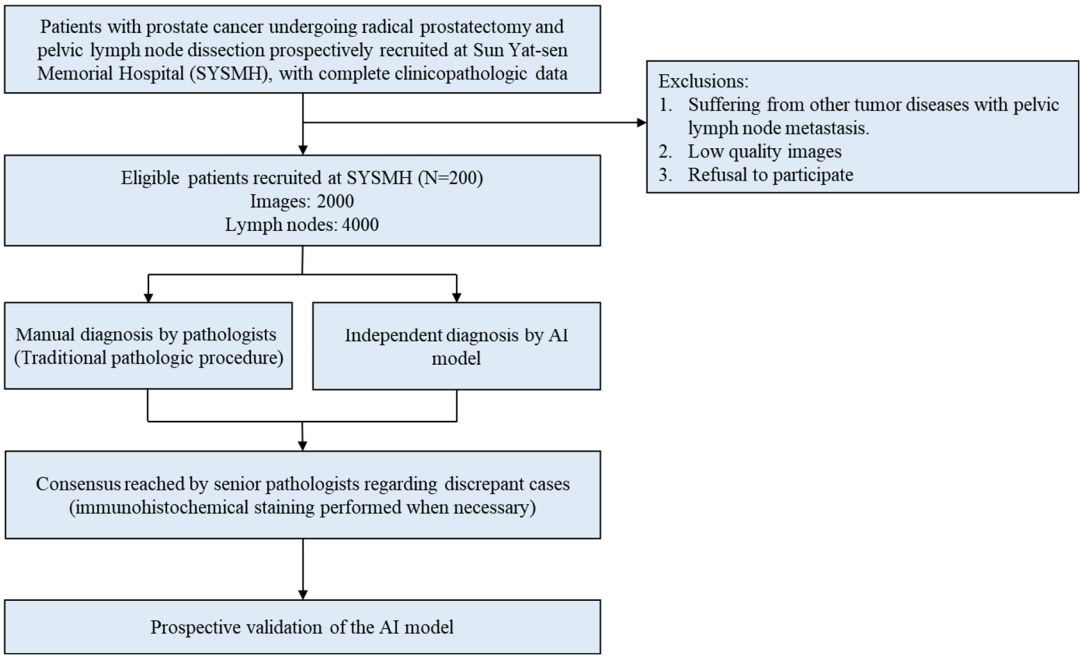
III. Research purpose

To evaluate the diagnostic performance and application value of the pre-developed AI diagnostic model for prostate cancer lymph node metastasis detection in real clinical

settings.

IV. Research design

The study is a prospective diagnostic trial and the flow chart of the study design is shown below:



V. Research Program and Technical Route

(i) Study population

Approximately 200 patients with prostate cancer in our center will be prospectively enrolled, and their lymph node pathological slides will be collected after pelvic lymphatic dissection.

1. Inclusion criteria

(1) Patients with prostate cancer who underwent radical prostatectomy and pelvic lymph node dissection;

(2) Complete clinical and pathological information.

2. Exclusion criteria

(1) Presence of other tumors with pelvic lymph node metastases;

(2) Low quality images;

(3) Patients refusing to participate in this research.

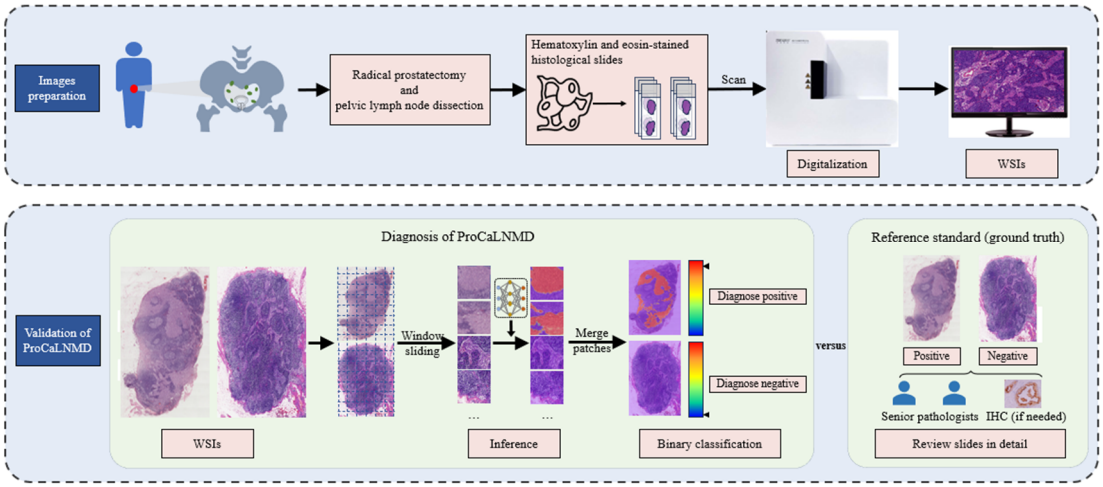
(ii) Data collection

1. Collect clinical and pathological data of the enrolled patients;

2. Digital whole slide images (WSI) of the patient's lymph node histopathological sections will be generated using a digital scanner. Low-quality images were eliminated from consideration. Approximately 10 lymph node pathology slides will be acquired from each patient who underwent radical prostatectomy with pelvic lymphatic dissection for prostate cancer, resulting in the collection of around 2000 pathologic lymph node images.

(iii) AI algorithm models

Capture the thumbnail of the Whole Slide Image (WSI) and delineate the organizational block region for classification. Employ a sliding window approach to traverse the tissue block region, generating patches of size 3*2028*2048 by moving from top to bottom and left to right. Input all the patches into the RegNetY_40 model, obtain the segmentation prediction probability for each patch, and convert the probabilities to 8-bit format (0~255). Set the probability threshold at 254, classifying pixels with a probability value equal to or greater than 254 as Tumor pixels. Calculate the count of tumor pixels within the WSI, using a number threshold of 0. If the number of pixels in the cancer category within the WSI is greater than 0, classify the WSI as positive (indicating the presence of tumor lymphatic metastasis); otherwise, classify it as negative (indicating the absence of tumor lymphatic metastasis). The flowchart is shown below:



(iv) Indicators for evaluating the results of the study

1. Accuracy: Ratio of the combined number of true-positive and true-negative cases predicted by the AI model to the total number of cases tested.
2. Sensitivity: Ratio of positive cases identified by the AI model to the number of positive cases confirmed by the gold standard.
3. Specificity: Ratio of negative cases identified by the AI model to the number of negative cases confirmed by the gold standard.

(v) Informed consent

The study, titled " Prospective Validation of Pathology-based Artificial Intelligence Diagnostic Model for Lymph Node Metastasis in Prostate Cancer," is a diagnostic trial devoid of interventions. Prior to the enrollment of each patient, and before they undergo the scheduled procedure, the researcher provides a comprehensive introduction to the protocol, purpose, procedures, associated costs, potential benefits, possible risks, confidentiality measures, and the patient's rights within the trial. Subsequently, an informed consent form is distributed to the patient, and enrollment in the study occurs only after the patient has signed the informed consent.

(vi) Ethical requirements

The study adhered to the guidelines outlined in the Good Clinical Research Practice

and the Declaration of Helsinki. Before the commencement of the trial, the protocol received approval from the hospital's Ethics Committee. In the event that a revision to the protocol becomes necessary during the study, the updated version must be resubmitted for review by the Ethics Committee. The investigator is required to await approval from the Ethics Committee before implementing any modifications to the protocol

In the course of this study, clinical data and personal information from research participants will be gathered for scientific research purposes, potentially implicating the privacy rights of the patients. To safeguard confidentiality, participants and data analysts involved in the study will be required to sign a confidentiality agreement. This agreement ensures that personal information and disease-related details of patients will not be disclosed to any individuals or organizations unrelated to the study. Stringent measures will be implemented to manage the collected patient data in a unified manner, mitigating the risk of personal information leakage.

VI. Security evaluation

None.

VII. Data collection and management

1. Study subjects

It is planned to prospectively enroll about 200 consecutive prostate cancer patients who need to undergo radical prostatectomy and pelvic lymph node dissection in our center from January 2024 to December 2025 for the validation of the AI model.

1.1 Inclusion criteria

(1) Patients with prostate cancer who underwent radical prostatectomy and pelvic lymph node dissection;

(2) Complete clinical and pathologic information.

1.2 Exclusion criteria

(1) Presence of other tumors that metastasize to the pelvic lymph nodes;

(2) Low quality images;

(3) Patients refusing to be enrolled.

2. Data collection

2.1 Clinical and pathologic data were collected from the enrolled patients;

2.2 Digitally scanning the pathologic histological sections of the patient's postoperatively resected lymph nodes. Approximately 10 lymph node pathology slides will be acquired from each patient, resulting in the collection of around 2000 pathological lymph node images.

VIII. quality management program

(i) Measures to improve consistency of observations

1. Every researcher involved in this project must undergo pre-study training to ensure a comprehensive understanding of the research program and the specific implications of its indicators. This initiative aims to enhance both intra-observer and inter-observer consistency among the clinical research data collectors, ultimately ensuring the reliability of the clinical research conclusions.

2. Each clinical research unit is expected to appoint an individual responsible for regularly monitoring the progress of the clinical research. This designated person will meticulously verify data and records to maintain the accuracy and integrity of the research findings.

(ii) Measures to ensure subject compliance

The subject profile must be strictly controlled for variables through the following measures:

1. Consistent involvement of physicians in clinical studies within each unit.
2. Researchers are required to diligently elucidate the informed consent of enrolled patients. This ensures a comprehensive understanding of the trial study's processes and the associated obligations of cooperation, thereby fostering active participation in the trial.

(iii) Monitoring of clinical trials

Competent monitors, designated by the sponsor, are tasked with conducting routine monitoring activities both before, during, and after the trial. This ensures strict adherence to all aspects of the research protocol and meticulous scrutiny of the source material.

IX. Pre-assessment of project risk benefits and risk control plan

Potential Benefits: Expected to assist pathologists in reducing missed diagnosis of lymph node micrometastases; No potential risk.

X. References

1 Sung, H. *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* **71**, 209-249, doi:10.3322/caac.21660 (2021).

2 Prado, K., Zhang, K. X., Pellegrini, M. & Chin, A. I. Sequencing of cancer cell subpopulations identifies micrometastases in a bladder cancer patient. *Oncotarget* **8**, 45619-45625, doi:10.18632/oncotarget.17312 (2017).

3 Shao, D. *et al.* Artificial intelligence in clinical research of cancers. *Brief Bioinform* **23**, doi:10.1093/bib/bbab523 (2022).

4 Ehteshami Bejnordi, B. *et al.* Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer. *Jama* **318**, 2199-2210, doi:10.1001/jama.2017.14585 (2017).