LEarning biOchemical Prostate cAncer Recurrence from histopathology sliDes : Structured description of the challenge design

CHALLENGE ORGANIZATION

Title

Use the title to convey the essential information on the challenge mission.

LEarning biOchemical Prostate cAncer Recurrence from histopathology sliDes

Challenge acronym

Preferable, provide a short acronym of the challenge (if any).

LEOPARD

Challenge abstract

Provide a summary of the challenge purpose. This should include a general introduction in the topic from both a biomedical as well as from a technical point of view and clearly state the envisioned technical and/or biomedical impact of the challenge.

Prostate cancer, impacting 1.4 million men annually, is a prevalent malignancy [1]. A substantial number of these individuals undergo prostatectomy as the primary curative treatment. The efficacy of this surgery is assessed, in part, by monitoring the concentration of prostate-specific antigen (PSA) in the bloodstream. While the role of PSA in prostate cancer screening is debatable [2,3], it serves as a valuable biomarker for postprostatectomy follow-up in patients. Following successful surgery, PSA concentration is typically undetectable (<0.1 ng/mL) within 4-6 weeks [4]. However, approximately 30% of patients experience biochemical recurrence, signifying the resurgence of prostate cancer cells. This recurrence serves as a prognostic indicator for progression to clinical metastases and eventual prostate cancer-related mortality [5,6,7,8].

Current clinical practices gauge the risk of biochemical recurrence by considering the International Society of Urological Pathology (ISUP) grade, PSA value at diagnosis, and TNM staging criteria [9]. A recent European consensus guideline suggests categorizing patients into low-risk, intermediate-risk, and high-risk groups based on these factors [10]. Notably, a high ISUP grade independently assigns a patient to the intermediate (grade 2/3) or high-risk group (grade 4/5).

The Gleason growth patterns, representing morphological patterns of prostate cancer, are used to categorize cancerous tissue into ISUP grade groups [11,12,13,14]. However, the ISUP grade has limitations, such as grading disagreement among pathologisdts[14] and being coarse descriptors of tissue morphology.

Recently, deep learning was shown [15] to be able to predict the biochemical recurrence of prostate cancer. Hypothesizing that deep learning could uncover finer morphological features' prognostic value, we are organizing the LEarning biOchemical Prostate cAncer Reccurance from histopathology sliDes (LEOPARD) challenge. The goal

of this challenge is to yield top-performance deep learning solutions to predict the time to biochemical recurrence from H&E-stained; histopathological tissue sections, i.e. based on morphological features.

Challenge keywords

List the primary keywords that characterize the challenge.challenge_

prostate cancer, biochemical recurrence, cancer survival

Year

The challenge will take place in 2024

FURTHER INFORMATION FOR CONFERENCE ORGANIZERS

Workshop

If the challenge is part of a workshop, please indicate the workshop.

N/A

Duration

How long does the challenge take?

Half day.

Expected number of participants

Please explain the basis of your estimate (e.g. numbers from previous challenges) and/or provide a list of potential participants and indicate if they have already confirmed their willingness to contribute.

validation phase: 50 teams,
testing phase: 10-20 teams

Publication and future plans

Please indicate if you plan to coordinate a publication of the challenge results.

An overview paper will be written with the organizing team's members. Each participating team who presented their method at the challenge session is allowed up to three co-authorships. The participating teams are encouraged to publish their results separately elsewhere when citing the overview paper after its publication.

Space and hardware requirements

Organizers of on-site challenges must provide a fair computing environment for all participants. For instance, algorithms should run on the same computing platform provided to all.

The challenge will be held via grand-challenge.org, thus participating teams will have a fair computing environment. For the half-day event during the conference, we would need a stable high-speed internet connection, projector, loud speakers and a microphone.

TASK 1: Predicting biochemical recurrence of prostate cancer from histopathology slides

SUMMARY

Abstract

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Keywords

List the primary keywords that characterize the task.

prostate cancer, biochemical recurrence, cancer survival, deep learning

ORGANIZATION

Organizers

a) Provide information on the organizing team (names and affiliations).

Khrystyna Faryna, Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands;
Clement Grisi, Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands;
Vittorio Augusti, University of Brescia, Brescia, 25121, Italy;
Joep Bogaerts, Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands;
Prof. Solen-Florence Kammerer Jaquet, Rennes University Hospital, Department of Pathology, Rennes, 35000, France;
Pierre Allaume, Rennes University Hospital, Department of Pathology, Rennes, 35000, France;
Prof. Jeroen van der Laak, Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands;
Prof. Geert Litjens, Department of Pathology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

b) Provide information on the primary contact person.

Khrystyna Faryna, khrystyna.faryna@radboudumc.nl

Life cycle type

Define the intended submission cycle of the challenge. Include information on whether/how the challenge will be continued after the challenge has taken place.Not every challenge closes after the submission deadline (one-time event). Sometimes it is possible to submit results after the deadline (open call) or the challenge is repeated with some modifications (repeated event).

Examples:

- One-time event with fixed conference submission deadline
- Open call (challenge opens for new submissions after conference deadline)
- Repeated event with annual fixed conference submission deadline

Repeated event with annual fixed conference submission deadline

Challenge venue and platform

a) Report the event (e.g. conference) that is associated with the challenge (if any).

MICCAI 2024 (if accepted)

b) Report the platform (e.g. grand-challenge.org) used to run the challenge.

grand-challenge.org

c) Provide the URL for the challenge website (if any).

Our challenge will be hosted at https://leopard.grand-challenge.org

Participation policies

a) Define the allowed user interaction of the algorithms assessed (e.g. only (semi-) automatic methods allowed).

Only fully automated methods are allowed.

b) Define the policy on the usage of training data. The data used to train algorithms may, for example, be restricted to the data provided by the challenge or to publicly available data including (open) pre-trained nets.

The usage of publicly available data including pre-trained models available under a permissive license (within the active phase of a challenge) is allowed, as long as participants clearly state their source and use-case, in each submission.

c) Define the participation policy for members of the organizers' institutes. For example, members of the organizers' institutes may participate in the challenge but are not eligible for awards.

Members of the organizers' institutes who are not associated with the challenge can participate in the challenge, but are not eligible for any awards and will be excluded from the final ranking.

d) Define the award policy. In particular, provide details with respect to challenge prizes.

The top 10 teams will be invited to be part of the challenge manuscript. In addition, we are actively seeking sponsorship for awards.

e) Define the policy for result announcement.

Examples:

- Top 3 performing methods will be announced publicly.
- Participating teams can choose whether the performance results will be made public.

1) All results will be announced publicly through a public leaderboard and each participating team will receive the model validation results after the submission. Only the team that submits the method description paper will be eligible for the final ranking.
2) The organizers encourage publicly available code submissions.

f) Define the publication policy. In particular, provide details on ...

- ... who of the participating teams/the participating teams' members qualifies as author
- ... whether the participating teams may publish their own results separately, and (if so)
- ... whether an embargo time is defined (so that challenge organizers can publish a challenge paper first).

An overview paper will be written with the organizing team's members. Each participating team who presented their method at the challenge session is allowed up to three co-authorships. The participating teams are encouraged to publish their results separately elsewhere when citing the overview paper after its publication.

Submission method

a) Describe the method used for result submission. Preferably, provide a link to the submission instructions.

Examples:

- Docker container on the Synapse platform. Link to submission instructions: <URL>
- Algorithm output was sent to organizers via e-mail. Submission instructions were sent by e-mail.

Interested teams must join the LEOPARD challenge at https://leopard.grand-challenge.org. After the release of the training dataset, they can start developing and training AI models using their private or public computing resources. The teams can submit a trained algorithm (a Docker container) for evaluation on a validation cohort. During evaluation, algorithms are executed on the grand-challenge.org platform, their performance is estimated on the hidden tuning cohort, and team rankings are updated accordingly on a live, public leaderboard. The top 10 teams based on validation cohort performance will be invited to submit their algorithm Docker containers for prediction on a testing set. Instructions for submitting AI models encapsulated in Docker containers to the Grand Challenge platform: https://grand-challenge.org/documentation/creating-an-algorithm-container/
In addition, we will provide baseline models with open-source training code and example inference Docker containers.

b) Provide information on the possibility for participating teams to evaluate their algorithms before submitting final results. For example, many challenges allow submission of multiple results, and only the last run is officially counted to compute challenge results.

Participants will be allowed to validate their results multiple times (up to 5) on a validation set before submitting the final results. This can also help participants ensure the submission is in the correct format. Only the best submission will be counted for the official validation ranking. Only a single test set submission will be allowed to avoid overfitting.

Challenge schedule

Provide a timetable for the challenge. Preferably, this should include

- the release date(s) of the training cases (if any)
- the registration date/period
- the release date(s) of the test cases and validation cases (if any)
- the submission date(s)
- associated workshop days (if any)
- the release date(s) of the results

- Announcement of challenge's opening: April 10th 2024
- Open for registration: April 10th, 2024
- Training data release: April 10th, 2024
- Validation phase start: July 1st, 2024
- Deadline for test set submission: August 1st, 2024
- Winner and invitation speakers: No later than August 28th, 2024

Ethics approval

Indicate whether ethics approval is necessary for the data. If yes, provide details on the ethics approval, preferably institutional review board, location, date and number of the ethics approval (if applicable). Add the URL or a reference to the document of the ethics approval (if available).

The Medical Ethics Committee of Radboud University Medical Center approved this challenge protocol on 5/1/2016, with NO. 20162275. Contact person: Geert Litjens, Department of Pathology, Radboud Institue for Health Science, Radboud University Medical Center, Nijmegen, The Netherlands; geert.litjens@radboudumc.nl

Data usage agreement

Clarify how the data can be used and distributed by the teams that participate in the challenge and by others during and after the challenge. This should include the explicit listing of the license applied.

Examples:

- CC BY (Attribution)
- CC BY-SA (Attribution-ShareAlike)
- CC BY-ND (Attribution-NoDerivs)
- CC BY-NC (Attribution-NonCommercial)
- CC BY-NC-SA (Attribution-NonCommercial-ShareAlike)
- CC BY-NC-ND (Attribution-NonCommercial-NoDerivs)

CC BY-NC-SA

Code availability

a) Provide information on the accessibility of the organizers' evaluation software (e.g. code to produce rankings). Preferably, provide a link to the code and add information on the supported platforms.

The evaluation pipeline will be made public and open source after the launch of the challenge. We will provide a GitHub link for the code of evaluation metrics on the challenge website.

b) In an analogous manner, provide information on the accessibility of the participating teams' code.

The participants are encouraged to upload their code to Github and share the Github link in the PDF submission file.

Conflicts of interest

Provide information related to conflicts of interest. In particular provide information related to sponsoring/funding of the challenge. Also, state explicitly who had/will have access to the test case labels and when.

There is no explicit sponsoring/funding of the challenge, but we aim to contact technology companies with an interest in the prostate cancer prognosis challenge. Only organizing members of the challenge have access to the test case labels during and after the LEOPARD challenge.

MISSION OF THE CHALLENGE

Field(s) of application

State the main field(s) of application that the participating algorithms target.

Examples:

- Diagnosis
- Education
- Intervention assistance

- Intervention follow-up
- Intervention planning
- Prognosis
- Research
- Screening
- Training
- Cross-phase
-

Prognosis

Task category(ies)

State the task category(ies)

Examples:

- Classification
- Detection
- Localization
- Modeling
- Prediction
- Reconstruction
- Registration
- Retrieval
- Segmentation
- Tracking

Prediction, Regression

Cohorts

We distinguish between the target cohort and the challenge cohort. For example, a challenge could be designed around the task of medical instrument tracking in robotic kidney surgery. While the challenge could be based on ex vivo data obtained from a laparoscopic training environment with porcine organs (challenge cohort), the final biomedical application (i.e. robotic kidney surgery) would be targeted on real patients with certain characteristics defined by inclusion criteria such as restrictions regarding sex or age (target cohort).

a) Describe the target cohort, i.e. the subjects/objects from whom/which the data would be acquired in the final biomedical application.

The target cohort consists of biological males, 50 years old and above who underwent prostatectomy after prostate cancer diagnosis.

b) Describe the challenge cohort, i.e. the subject(s)/object(s) from whom/which the challenge data was acquired.

The challenge cohort consists of biological males, 50 years old and above who underwent prostatectomy after prostate cancer diagnosis.

Imaging modality(ies)

Specify the imaging technique(s) applied in the challenge.

Brightfield H&E; stained histopathology

Context information

Provide additional information given along with the images. The information may correspond ...

a) ... directly to the image data (e.g. tumor volume).

The histopathology slides (*****.tif format, where ***** stands for subject_id) that were collected in different real-life scenarios. The annotation would be provided as a .csv file with three columns: subject_id, recurrence_event, time_to_recurrence_in_months.

b) ... to the patient in general (e.g. sex, medical history).

N/A

Target entity(ies)

a) Describe the data origin, i.e. the region(s)/part(s) of subject(s)/object(s) from whom/which the image data would be acquired in the final biomedical application (e.g. brain shown in computed tomography (CT) data, abdomen shown in laparoscopic video data, operating room shown in video data, thorax shown in fluoroscopy video). If necessary, differentiate between target and challenge cohort.

H&E; stained histopathology slide of a prostate.

b) Describe the algorithm target, i.e. the structure(s)/subject(s)/object(s)/component(s) that the participating algorithms have been designed to focus on (e.g. tumor in the brain, tip of a medical instrument, nurse in an operating theater, catheter in a fluoroscopy scan). If necessary, differentiate between target and challenge cohort.

The participating algorithms will be designed to predict the time to biochemical recurrence in months from an H&E; stained histopathology slide of a prostate.

Assessment aim(s)

Identify the property(ies) of the algorithms to be optimized to perform well in the challenge. If multiple properties are assessed, prioritize them (if appropriate). The properties should then be reflected in the metrics applied (see below, parameter metric(s)), and the priorities should be reflected in the ranking when combining multiple metrics that assess different properties.

- Example 1: Find highly accurate liver segmentation algorithm for CT images.
- Example 2: Find lung tumor detection algorithm with high sensitivity and specificity for mammography images.

Corresponding metrics are listed below (parameter metric(s)).

Accuracy, robustness, generalizability, interpretability, usability, and applicability.

DATA SETS

Data source(s)

a) Specify the device(s) used to acquire the challenge data. This includes details on the device(s) used to acquire the imaging data (e.g. manufacturer) as well as information on additional devices used for performance assessment (e.g. tracking system used in a surgical setting).

3D HISTECH PANNORAMIC 1000 histopathology slide scanner.

b) Describe relevant details on the imaging process/data acquisition for each acquisition device (e.g. image acquisition protocol(s)).

The slides were scanned at a resolution of 0.5 micrometers per pixel.

c) Specify the center(s)/institute(s) in which the data was acquired and/or the data providing platform/source (e.g. previous challenge). If this information is not provided (e.g. for anonymization reasons), specify why.

The training set originates from Radboud University Medical Center and TCGA. The test set was obtained from Radboud University Medical Center as well as several anonymous institutions.

d) Describe relevant characteristics (e.g. level of expertise) of the subjects (e.g. surgeon)/objects (e.g. robot) involved in the data acquisition process (if any).

Automatic staining protocol.

Training and test case characteristics

a) State what is meant by one case in this challenge. A case encompasses all data that is processed to produce one result that is compared to the corresponding reference result (i.e. the desired algorithm output).

Examples:

- Training and test cases both represent a CT image of a human brain. Training cases have a weak annotation (tumor present or not and tumor volume (if any)) while the test cases are annotated with the tumor contour (if any).
- A case refers to all information that is available for one particular patient in a specific study. This information always includes the image information as specified in data source(s) (see above) and may include context information (see above). Both training and test cases are annotated with survival (binary) 5 years after (first) image was taken.

Training and test cases both represent a histopathology slide of a prostate. Training and test cases have a weak annotation representing the recurrence event and the time from prostatectomy to the recurrence of the disease in months.

b) State the total number of training, validation and test cases.

The dataset consists of +/-500 training slides, +/-100 validation, and +/-1300 test slides.

c) Explain why a total number of cases and the specific proportion of training, validation and test cases was chosen.

The external 1100 slides will only be used for testing. The internal 800 slides have been split into 500 training, 100 validation, 200 testing slides (a split commonly used in literature).

d) Mention further important characteristics of the training, validation and test cases (e.g. class distribution in classification tasks chosen according to real-world distribution vs. equal class distribution) and justify the choice.

The training data has real-world distribution. Participants should expect data with domain shift/from other institutions in validation and testing. We encourage participants to develop models that generalize well across centers despite domain shift caused by differences in staining and scanners in histopathology. At the same time, we will try to match important characteristics of the development and testing cohorts as far as possible, for example, age, Gleason grades, etc.

Annotation characteristics

a) Describe the method for determining the reference annotation, i.e. the desired algorithm output. Provide the information separately for the training, validation and test cases if necessary. Possible methods include manual image annotation, in silico ground truth generation and annotation by automatic methods.

If human annotation was involved, state the number of annotators.

Not applicable.

b) Provide the instructions given to the annotators (if any) prior to the annotation. This may include description of a training phase with the software. Provide the information separately for the training, validation and test cases if necessary. Preferably, provide a link to the annotation protocol.

Not applicable.

c) Provide details on the subject(s)/algorithm(s) that annotated the cases (e.g. information on level of expertise such as number of years of professional experience, medically-trained or not). Provide the information separately for the training, validation and test cases if necessary.

Not applicable.

d) Describe the method(s) used to merge multiple annotations for one case (if any). Provide the information separately for the training, validation and test cases if necessary.

Not applicable.

Data pre-processing method(s)

Describe the method(s) used for pre-processing the raw training data before it is provided to the participating teams. Provide the information separately for the training, validation and test cases if necessary.

Each slide was resampled to include 0.5, 2.0, 8.0 microns/pixel resolution. Slide packing was used to reduce the slide size. The average slide size is approximately 2.0 GB.

Sources of error

a) Describe the most relevant possible error sources related to the image annotation. If possible, estimate the magnitude (range) of these errors, using inter-and intra-annotator variability, for example. Provide the information separately for the training, validation and test cases, if necessary.

Not applicable.

b) In an analogous manner, describe and quantify other relevant sources of error.

Not entire prostate tissue histopathology is available for each case. It is possible that some more aggressive parts that correlate with a higher chance of recurrence were not represented in some cases. Such limitation is a consequence of the histopathology tissue processing routines in labs.

ASSESSMENT METHODS

Metric(s)

a) Define the metric(s) to assess a property of an algorithm. These metrics should reflect the desired algorithm properties described in assessment aim(s) (see above). State which metric(s) were used to compute the ranking(s) (if any).

- Example 1: Dice Similarity Coefficient (DSC)
- Example 2: Area under curve (AUC)

C-index

b) Justify why the metric(s) was/were chosen, preferably with reference to the biomedical application.

The concordance index (C-index) quantifies the model's ability to provide an accurate ranking of the survival times based on the computed individual risk scores, generalizing the area under the receiver operating curve (AUROC).
It is a standard metric for the assessment and comparison of survival/recurrence prediction models.
It can account for censored data and represents the global assessment of the model discrimination power.

Ranking method(s)

a) Describe the method used to compute a performance rank for all submitted algorithms based on the generated metric results on the test cases. Typically the text will describe how results obtained per case and metric are aggregated to arrive at a final score/ranking.

The C-index is a widely used metric for survival analysis which allows taking into account time-to-event information and censored data.

b) Describe the method(s) used to manage submissions with missing results on test cases.

We will exclude the participants who fail to report on the whole testing set.

c) Justify why the described ranking scheme(s) was/were used.

For each test case, we will calculate the C-index between the ground truth and the results from the participants across all testing images. The ranking will be based on the C-index value obtained on the test cohort.

Statistical analyses

a) Provide details for the statistical methods used in the scope of the challenge analysis. This may include

- description of the missing data handling,
- details about the assessment of variability of rankings,
- description of any method used to assess whether the data met the assumptions, required for the particular statistical approach, or
- indication of any software product that was used for all data analysis methods.

A bootstrap will be performed on the test set to evaluate the variance of the C-index of each team and for statistical comparison of algorithm results.
The log-rank test will be used to assess the significance of Kaplan-Meier statistics. The python SciPy and Scikit-learn libraries will be used for the statistical analyses.

b) Justify why the described statistical method(s) was/were used.

The bootstrap analysis allows us to simulate different sampling of the test set to approximate the variance of the C-index.

Further analyses

Present further analyses to be performed (if applicable), e.g. related to

- combining algorithms via ensembling,
- inter-algorithm variability,
- common problems/biases of the submitted methods, or
- ranking variability.

These further analyses will be discussed in a publication after the challenge.

ADDITIONAL POINTS

References

Please include any reference important for the challenge design, for example publications on the data, the annotation process or the chosen metrics as well as DOIs referring to data or code.

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. https://doi.org/10.3322/caac.21660 (2021).
2. Grossman, D. C. et al. Screening for Prostate Cancer: US preventive services task force recommendation statement. JAMA 319, 1901-1913 (2018).
3. Heijnsdijk, E. A. M. et al. Summary statement on screening for prostate cancer in Europe. Int J Cancer 142, 741-746 (2018).
4. Goonewardene, S. S., Phull, J. S., Bahl, A. &, Persad, R. A. Interpretation of PSA levels after radical therapy for prostate cancer. Trends Urol. Men S Health 5, 30-34 (2014).
5. Amling, C. L. et al. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol. 164, 101-105 (2000).
6. Freedland, S. J. et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294, 433-439 (2005).
7. Han, M., Partin, A. W., Pound, C. R., Epstein, J. I. & Walsh, P. C. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Ur. Clin. North Am. 28, 555-565 (2001).
8. Van den Broeck, T. et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. Eur. Urol. 75, 967-87. (2019).
9. Epstein, J. I. et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am. J. Surg. Pathol. 40, 244-252 (2016).
10. Mottet, N. et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur. Urol. 79, 243-62. (2021).
11. Epstein, J. I. An update of the Gleason grading system. J. Urol. 183, 433-440 (2010).
12. Pierorazio, P. M., Walsh, P. C., Partin, A. W. & Epstein, J. I. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 111, 753-60. (2013).

13. Epstein, J. I. et al. A Contemporary Prostate Cancer Grading System: a validated alternative to the Gleason score. Eur. Urol. 69, 428-35. (2016).

Further comments

Further comments from the organizers.

N/A