Deep Learning-based Method for Spermatogenic Staging and Assessing Testicular Toxicity Endpoints in Rats

• 9th Digital Pathology & AI Congress • London, UK • 7-8th December, 2022

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Introduction

Exposure to drugs and chemicals has significant adverse effects on the reproductive system. Histopathologic evaluation of the testis is an important component when assessing drug safety and environmental toxicants. To identify drug related changes, reproductive toxicity studies are conducted using animals and the outcome is extrapolated to human toxicity. Understanding the cellular relationships occurring during the spermatogenic cycle (stage-aware evaluation) helps recognize absent cells and detect subtle changes restricted to specific points in spermatogenesis. Earlier, we[1] had developed a deep learning (DL) based method to automate the staging which is easy to use, and provides results comparable to an expert on normal testes and to historical data[2]. Taking this ahead, we propose a DL-based approach for the identification and quantification of the stage-specific and non-specific endpoints in rat testis viz. spermatid retention, tubular degeneration, germ cells degeneration, vacuolation, dilation etc.

Materials and Methods

We created a training dataset consisting of 8,000 image tiles of size 512x512 which was used for segmenting out tubules, germ cells, and various non-proliferative lesions[3]. We extracted these tiles from 20 Whole Slide Images (WSIs).

We have trained multiple variants of U-Net based deep learning networks on this for semantic segmentation of various parameters. The details of the parameters and network architectures used are as given in the table 1. We have shown the network architecture for Hist Net model in Fig. 1.

Germ cells (Round Spermatids, Elongated Spermatids, Meiotic Bodies, Round Spermatids in Stage X, Spermatogonia, Spermatocytes)	Degeneration/ Necrosis	Degeneration, Tubular	Vacuolation	Multinucleated Giant Cells
HistNet[4], YAMU-Net[5]	HistNet, EfficientNet, YAMU-Net	HistNet	YAMU-Net	EfficientNet

Table 1. Network Details

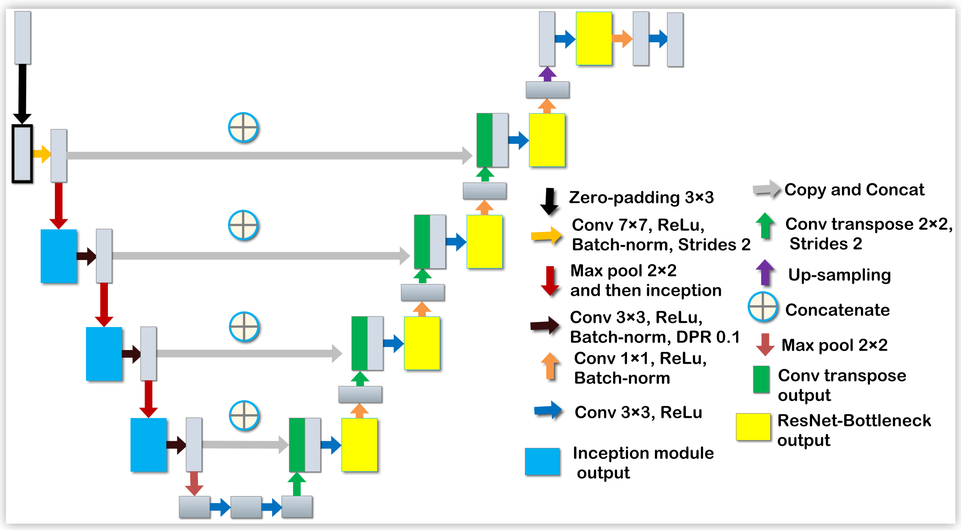

Fig. 1. Hist Net model architecture used for the germ cell segmentation tasks

Spermatogenic staging

The workflow of the staging assessment algorithm is as shown in Fig. 2. This is part of our published work in 2021[1]. For identification of stage-specific lesions, group staging assessment was performed on the tubules.

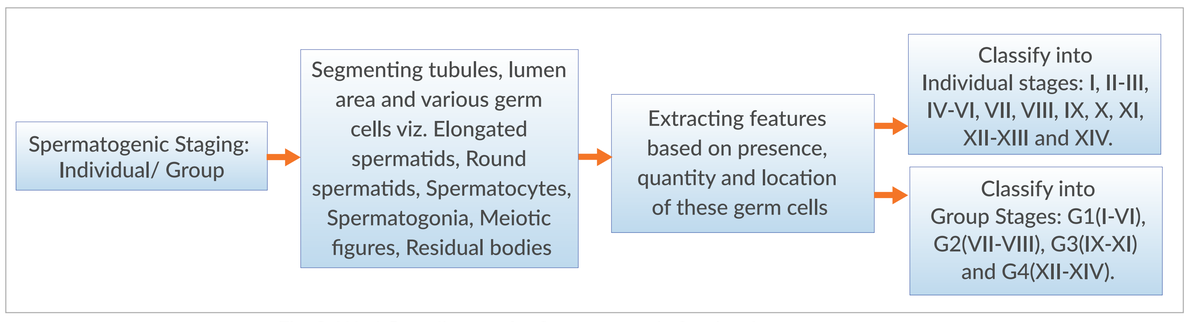

Fig. 2. Workflow diagram for Spermatogenic Staging Assessment

Lesion detection

First, we perform the group staging assessment for the identification of stage-specific lesions. A rule-based approach was then applied for the detection of stage-specific lesions viz. spermatid retention in group G3 (Stage IX-XI) & group G4 (Stage XII-XIV) stages and germ cell degeneration specific to particular group stages. The workflow for the lesion detection is as drawn in Fig. 3. Validation was performed on a test dataset of 179 WSIs of rodent testis sections.

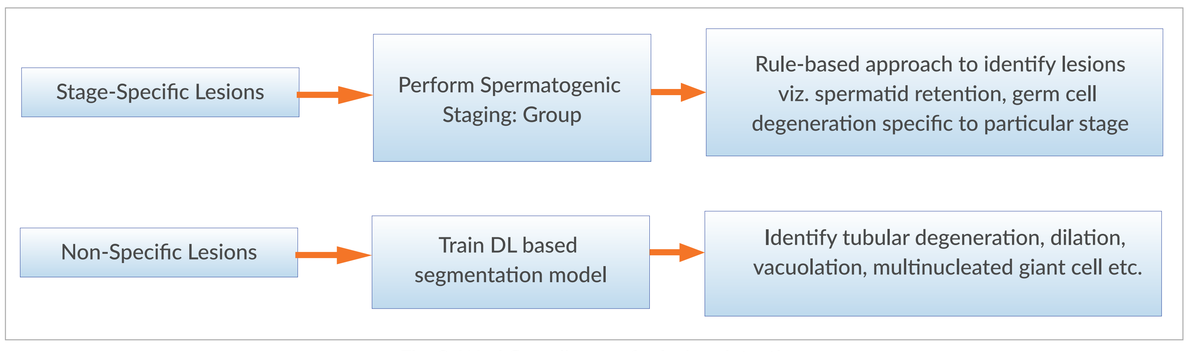

Fig. 3. Workflow diagram for lesion detection

Results

We have selected 7502 tubules from 30 whole slide images for the validation of spermatogenic staging algorithm. A screenshot of the spermatogenic staging assessment is as shown in figure 4. We have also compared the stage frequency maps generated by the proposed method with expert pathologists[1] and that published in literature[2]. This comparison is shown in Fig 5.

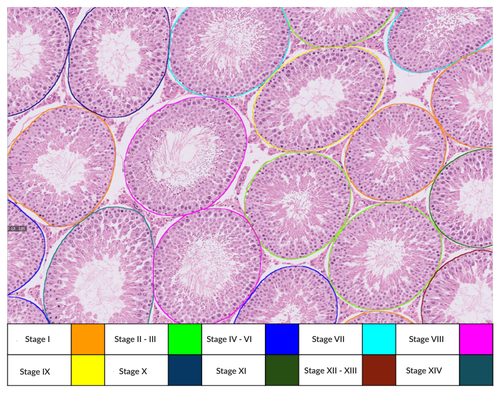

Fig. 4. Annotation for Spermatogenic Staging Assessment

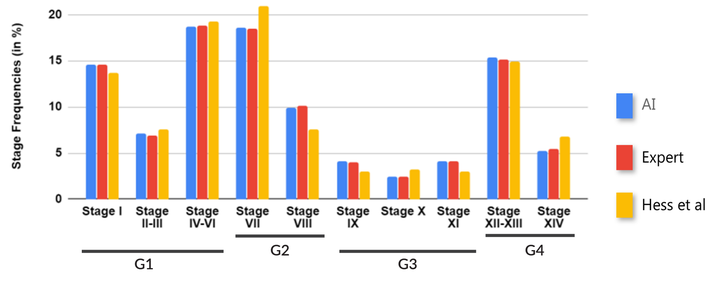

Fig. 5. Stage Frequency Maps Comparison

For validation of the lesion detection results, slide level findings provided by pathologists based on data from two nonclinical studies were compared with the algorithms' results. Quantitative outputs of the algorithm correlated well with the grades provided by pathologists. These results are as listed in table 2.

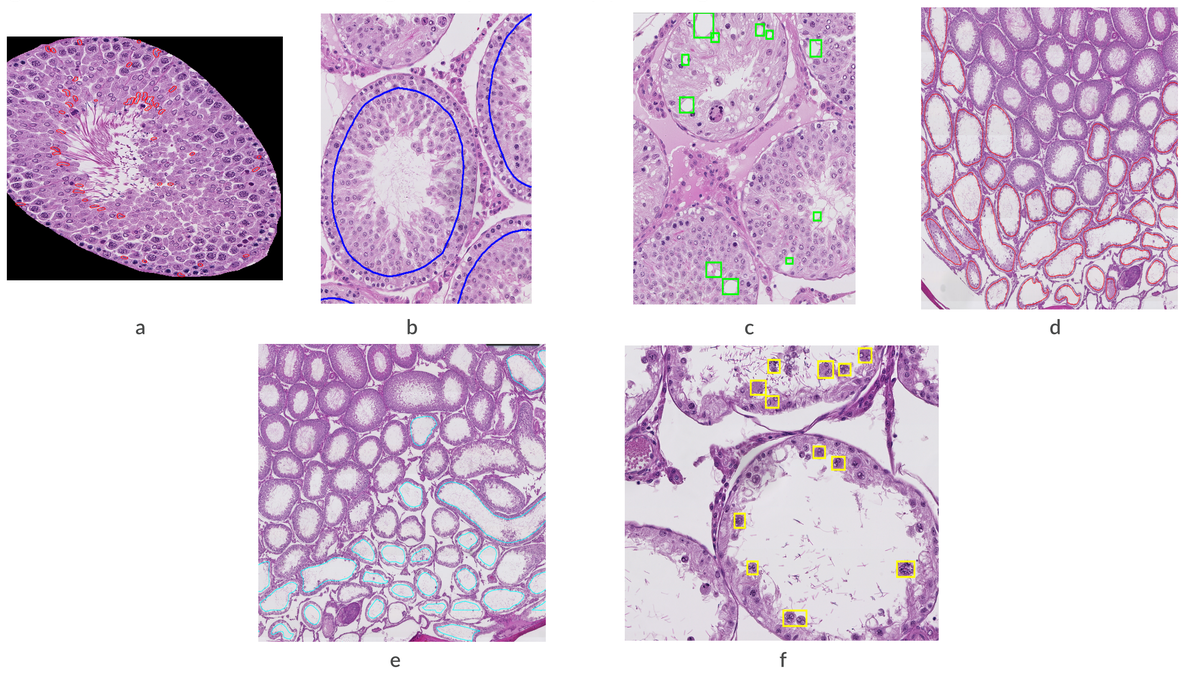

Fig. 6. DL recognition outputs; a) Spermatid retention; b) Degeneration, germ cell; c) Vacuolation; d) Degeneration, tubular; e) Dilation; f) Multinucleated giant cell

Lesion	Accuracy (%)	Sensitivity (%)	Specificity (%)
Degeneration, Tubular	100	100	100
Degeneration, Germ Cell	94.4	70.0	97.4
Dilation	100	100	100
Spermatid Retention	97.8	100	97.1
Vacuolation	95.5	100	95.3

Table. 2. Lesion detection results

Conclusion

The solution provides an automated, objective and accurate method for assessment of toxicity changes occurring in rat testis. The proposed method can accurately detect and quantify spermatid retention and other lesions in testes sections that are otherwise healthy. This method addresses the challenges associated with the conventional qualitative/semi-quantitative method.

Impact Statement

The proposed solution facilitates assessment of the testis tissue in a stage-aware manner. The spermatogenic staging solution can not only stage tubules much more efficiently compared to manual staging, but also provide objective and reproducible outputs. The quantitative nature of the complete solution has the potential to change the paradigm in the pathologist's workflow. The proposed method can capture the subtle changes occurring in the testis which otherwise can be easily missed. Further, the proposed solution can be compared easily with study specific/historical control data and literature reference ranges. This method can be generalized and extended to other species.

References

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