

Modern Diagnostic Approaches and Therapeutic Strategies for  
Ocular Surface Tumors

Ph.D. thesis

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## 1. Introduction

The human cornea constitutes the anterior segment of the eye's outer fibrous coat and is continuous with the sclera in a watch-glass-like configuration. The sclera is covered by the transparent and richly vascularized conjunctiva. Together, the cornea and conjunctiva form the ocular surface, which may be affected by certain benign and malignant neoplastic diseases. There are three types of ocular surface tumors: epithelial tumors (including melanocytic and non-melanocytic tumors), stromal tumors (vascular, fibrous, neural, histiocytic, myogenic, lipomatous, lymphoproliferative, choristoma), and secondary or metastatic tumors.<sup>1,2</sup> Although these tumors are rare; the incidence of ocular surface squamous neoplasia (OSSN) is 0.1-35 cases per 1,000,000 population, while the incidence of conjunctival melanoma is 0.06-1.5 cases per 1,000,000 population, they have a significant impact on patient morbidity and mortality.<sup>3</sup> Based on our clinical experience, malignant conjunctival tumors are being diagnosed at an increasingly younger age.<sup>3</sup>

Early and accurate diagnosis is essential for selecting the appropriate treatment modality and preventing further damage to health. Excisional biopsy followed by histopathological evaluation remains the gold standard diagnostic procedure, while diagnosis based on clinical examination is usually difficult and uncertain. High-resolution in vivo imaging modalities, such as in vivo confocal microscopy (IVCM) and anterior segment swept source optical coherence tomography (SS-OCT), enable real-time tissue- and cell-level visualization of biological systems, including the easily accessible cornea and conjunctiva.<sup>5,6</sup> In recent years, artificial intelligence (AI)-based automated systems have gained increasing prominence in ophthalmic diagnostics.

Traditionally, management of malignant ocular surface tumors has relied on surgical excision using a "no-touch" technique, combined with adjunctive cryotherapy.<sup>1,2</sup> However, due to the relatively high rate of recurrence and the potential risk of limbal stem cell deficiency associated with repeated surgical interventions, pharmacotherapy has become increasingly common.<sup>8</sup> Local pharmacotherapy (chemo- or immunotherapy) can be used either alone or in combination with surgical intervention.<sup>8,9</sup>

## **2. Aims**

The aim of our research is to provide a complex investigation of modern diagnostic and therapeutic options for ocular surface tumors, with a particular focus on ocular surface squamous neoplasia. The research aims to support diagnostic and therapeutic decisions in three complementary areas:

1. To conduct a systematic literature review and meta-analysis to compare the efficacy of surgical excision with topical pharmacotherapeutic agents, including interferon alpha (IFN), mitomycin C (MMC), and 5-fluorouracil (5-FU) in the treatment of OSSN. Based on these data, we analyzed disease course and treatment outcomes across the different therapeutic modalities.
2. To examine the role of swept-source optical coherence tomography in the differential diagnosis of ocular surface lesions, with particular emphasis on the differentiation of benign, inflammatory, and malignant processes. Comparison of the characteristics of various ocular surface lesions obtained with SS-OCT with histological results. The aim is to determine the diagnostic value of the technique and to identify predictive morphological markers.
3. To develop an artificial intelligence-based method using in vivo confocal microscopy to distinguish ocular surface squamous cell carcinoma from other ocular surface lesions, and compare the diagnostic performance of different known artificial intelligence-based algorithms.

### **2.1. Main hypotheses of the research**

1. We assume that topical pharmacotherapy, such as interferon alfa 2b, mitomycin C, and 5-fluorouracil, is an effective and safe treatment alternative for ocular surface tumors, especially ocular surface squamous neoplasia, in addition to surgical excision, which is the gold standard.
2. We hypothesize that swept-source OCT can identify structural abnormalities that allow differentiation between ocular surface tumors and non-neoplastic lesions, and that its quantitative parameters have predictive value in the diagnosis of OSSN.
3. We hypothesize that an artificial intelligence-based image processing algorithm can recognize microscopic patterns characteristic of OSSN in IVCN images, thereby supporting objective, rapid, and accurate diagnosis in clinical practice.

### **3. Materials and methods**

#### **3.1. Topical pharmacotherapy for ocular surface squamous neoplasia: systematic review and meta-analysis**

We conducted a meta-analysis using the population intervention-control-outcomes (PICO) method. We searched for studies in which patients were diagnosed with ocular surface squamous neoplasia (P). They were treated with either a local topical pharmacotherapy (IFN, MMC, or 5-FU) or surgical excision, and these two methods were compared (I and C). We examined clinical success, recurrence, and side effects (hyperaemia, pain, keratopathy with or without limbal stem cell deficiency, dry eye, and systemic diseases) for the different treatment methods.

##### *Search and selection method:*

A systematic search of the electronic databases Medline, Embase, and the Cochrane Central Register of Controlled Trials was performed to identify relevant publications, using a complex, multi-component search key, which we optimized during multiple searches.

Records identified through the search were imported into EndNote reference management software. After removal of duplicates, studies were screened based on title, abstract, and full text. The selection process was conducted independently by two reviewers.

Data collection from each publication was based on several criteria: number of cases, demographic data, treatment method, clinical success rate, recurrence, and complications.

The protocol was successfully registered in the PROSPERO database.

Comparative analysis between topical pharmacotherapy and surgical excision was performed based on clinical success and recurrence rates, and statistical analyses were performed on these. We presented our results using forest and funnel plots.

#### **3.2. Differential diagnostic importance of swept-source optical coherence tomography in ocular surface lesions**

The aim of this retrospective study was to analyze the characteristics of various ocular surface lesions using anterior segment optical coherence tomography and to compare these characteristics with histopathological results. Imaging of the anterior segment was performed using a high-resolution, swept-source Fourier domain OCT system (ANTERION, Heidelberg

Engineering, Heidelberg, Germany) with a 1310 nm wavelength laser source. In all cases, an incisional or excisional biopsy was performed, and the obtained samples were sent for histological examination. Histological sections were prepared with hematoxylin-eosin (H&E) staining, and Ki-67 and p40 markers were used for immunohistochemical (IHC) analysis. The clinical diagnosis based on slit lamp examination was compared with the optical coherence tomography characteristics of the lesion and with the histological results. In all cases, slit lamp examination and photographic documentation were performed and analyzed prior to review of the OCT images for the purpose of establishing a preliminary clinical diagnosis. Subsequently, the OCT evaluation was performed independently, without knowledge of the histological results. Histological analysis was performed as the final step in all cases. This step-by-step evaluation allowed for an unbiased comparison of the accuracy of each diagnostic method.

### **3.3. Application of artificial intelligence in the diagnosis of ocular surface squamous cell carcinoma using in vivo confocal microscopy**

Our database consisted of 2,774 IVCN images, which we classified into five categories: OSSN (745 images), normal cornea (1,559 images), melanoma (270 images), pterygium (115 images), and keratitis (85 images). The distribution per patient ensured that there was no overlap between the training and validation datasets, thus preventing overfitting and the model learning patient-specific characteristics. The OSSN group contained 745 images with OSSN lesions, while the non-OSSN group included pterygium, keratitis, conjunctival melanoma, and normal cornea; non-OSSN lesions were present in a total of 2,029 images. We trained three deep learning models: ResNet50V2, Yolov8x, and VGG19, and compared their performance. The goal was to distinguish between healthy and pathological IVCN images, classify OSSN-related signs ("starry sky," hyperkeratosis, mitosis, and enlarged irregular epithelial cells), find patient-specific markers in IVCN images, and classify cells with high accuracy.

To address the dataset imbalance, we developed a new square-based data augmentation strategy. We interpreted the decision processes of the models using Shapley values and Uniform Manifold Approximation and Projection (UMAP) analysis, thereby increasing the transparency of the algorithms.

## 4. Results

### 4.1. Topical pharmacotherapy for ocular surface squamous cell neoplasia: systematic review and meta-analysis

The literature search identified a total of 7,859 records. We performed duplicate screening manually and with the help of the reference management program, leaving 5,669 publications on the topic. We then selected articles individually based on their titles, leaving 1,129 articles. Subsequent abstract screening resulted in 59 full-text articles assessed for eligibility, of which 7 were included in the final analysis.

Data extraction was conducted systematically for each study, based on several criteria: number of cases, demographic data, treatment method, clinical success rate, recurrence, and complications.

Four studies were included in the qualitative synthesis, while three additional publications were included in the quantitative meta-analysis. A total of 159 patients diagnosed with ocular surface squamous neoplasia were included in the four cohort studies. A total of 318 patients were included in the quantitative synthesis. Those studies were selected for meta-analysis that compared surgical excision with topical pharmacotherapeutic treatment in terms of clinical success and recurrence. Three further studies were included in the qualitative assessment to enable comparison of different pharmacotherapeutic agents and their associated complications.

The results of the publications included in the meta-analysis were consistent. The statistical analysis showed no significant difference in clinical success between topical pharmacotherapy and surgical excision [odds ratio (OR): 0.785; confidence interval (CI): 0.130-4.736;  $p = 0.792$ ]. We found no significant difference between surgical excision and topical pharmacotherapy in terms of recurrence (OR: 0.746; CI: 0.213-2.609;  $p = 0.646$ ). The most commonly observed side effect was dry eye, regardless of the treatment method used. The highest incidence (59%) was observed in patients undergoing surgical excision.

#### **4.2. The differential diagnostic significance of swept-source optical coherence tomography in ocular surface lesions**

Thirty-seven patients (19 males and 18 females) with 38 eyes were included in the study. The average age was  $60.36 \pm 17.29$  years (ranging from 8 to 85 years). We performed excisional biopsies in 27 patients and incisional biopsies in 10 patients. Thirteen lesions were pigmented and 25 were non-pigmented. Based on the analysis of OCT images, 11 lesions affected the epithelium, of which 5 cases were confined only to epithelial involvement. In six cases, both the epithelium and subepithelium were affected, and in 27 cases, the lesion extended only to the subepithelium.

Concordance between histopathology and OCT findings was observed in 57% (6/11) of cases with epithelial involvement and in 84% (28/33) of cases with subepithelial involvement.

Clinical and histological diagnoses were consistent in 25 cases (65%), while in 13 cases (35%) the initial clinical impression differed from the final histopathological result. Of these 13 cases, the results of high-resolution OCT examination were consistent with the histological findings in 8 cases. In five cases, OCT did not influence the clinical suspicion based on slit lamp examination.

Based on histological examination, 7 tumors were found to be malignant (2 malignant melanomas, 3 conjunctival lymphomas, and 2 squamous cell carcinomas), while 4 lesions were premalignant (2 primary acquired melanoses and 2 corneal intraepithelial neoplasia). Three lesions proved to be inflammatory in origin, and the remaining cases were benign growths: 10 conjunctival nevi, 3 squamous cell papillomas, 5 pterygia, 2 conjunctival inclusion cysts, 1 granulation tissue, 1 Salzmann's nodular degeneration, 1 lymphangiectasia, and 1 conjunctival venous lake.

Corneal involvement was detected in ten lesions. Three lesions affected the fornix, another three affected the tarsal conjunctiva, while in four cases the lesion also reached the caruncle. Cystic lesions were observed in a total of 13 cases with different etiological backgrounds. In eight cases, the cysts were located intralesionally, while in five cases they were located extralesionally. Notably, in the six cases with combined epithelial and subepithelial involvement, the clinical and the histological diagnoses differed. This discrepancy was particularly evident in distinguishing benign from premalignant or malignant lesions. In two of these cases, OCT findings suggested the final histopathological diagnosis.

A subgroup analysis was performed to evaluate pigmented and non-pigmented lesions separately. The pigmented subgroup included 13 patients (6 males and 7 females) with a

mean age of  $40.07 \pm 21.65$  years (range: 8–75 years). Histological examination confirmed 10 benign, 2 premalignant, and 1 malignant lesions, including 9 conjunctival nevi, 1 venous lake, 2 primary acquired melanomas, and 1 atypical melanoma arising on the basis of PAM. The clinical and histological diagnoses matched in 11 cases, while in the remaining 2 cases, the OCT findings were consistent with the histological results.

In the non-pigmented subgroup, 25 patients were analyzed, including 13 males and 12 females, with a mean age of  $64.52 \pm 12.85$  years (range: 41–85 years). Histological evaluation identified 17 benign, 2 premalignant, and 6 malignant lesions. Diagnoses included 2 conjunctival cysts, 1 conjunctival nevus, 3 squamous cell papillomas, 5 pterygia, 3 inflammatory lesions, 1 lymphatic dilatation, 1 granulation tissue, 1 Salzmann's nodular degeneration, 2 conjunctival intraepithelial neoplasia, 2 squamous cell carcinoma, 3 lymphoma, and 1 amelanotic melanoma. The clinical and histological diagnoses matched in 14 cases, while in 6 of the remaining 11 cases, the OCT findings supported the histological diagnosis.

### **4.3. Application of artificial intelligence in the diagnosis of ocular surface squamous cell neoplasia using in vivo confocal microscopy**

#### *Classification results of healthy and unhealthy IVCM images*

In the first binary classification task, all three models (Resnet50V2, Yolov8x, and VGG19) achieved an accuracy above 90%. Both ResNet50V2 and Yolov8x showed an F1 score of 99%, while VGG19 produced more false negatives, which significantly reduced its F1 score.

#### *Classification results of OSSN-related signs*

By dividing the rectangle annotations into squares, we greatly improved the training and validation results, but the average accuracy of the model was still around 50%. We grouped all OSSN-related signs into one class, while non-OSSN-related signs formed the other class. With this approach, the ResNet50V2 model achieved 92% F1 accuracy, while Yolov8x achieved 95%. Although VGG19 produced the lowest F1 score in this task, its 89% performance is still considered acceptable.

#### *Classification results for patient-specific images*

All three models performed well in classifying patient-specific OSSN-diagnosed images. ResNet50V2 produced the highest F1 score, making it the model that focuses most on

patient-specific characteristics out of the three trained models. Meanwhile, VGG performed 14% worse in this task. ResNet50V2 gave the best results, while VGG19 gave the worst results in the classification task for healthy subjects. However, the differences between the models are much greater here. Based on these results, it appears that ResNet50V2 is the most sensitive to patient-specific characteristics. Yolov8x and VGG-19 may be less sensitive and may perform better on images that are more difficult to assign to specific patients.

#### *Cell-level classification results*

All three models produced values higher than 85% F1 scores. The best results were achieved by the VGG19 model with a 90% F1 score. The accuracy and loss curves of VGG19 did not show overfitting, so the training process was successful. Based on the results, models trained for cell-level classification are capable of producing the most stable results in the OSSN identification problem. The accuracy of our models was further improved by aggregating the cell-level results. All three models had F1 scores above 90%. As a result, OSSN images can be accurately distinguished from IVCN images that were not classified as healthy by cell-level classification. In this case, the performance metrics of the models showed very similar values.

#### *Shapley values*

Analysis of Shapley values showed that the model's decisions are not determined by individual pixels, but rather by global image characteristics. The most influential areas were the borders of the cells and the region of the nucleus, where color and shape information play a major role.

#### *UMAP analysis*

According to the UMAP analysis, the neural network's decisions are based on the combined effect of several factors. During the projections, the clusters were separated, but partial overlaps were observed, indicating that accurate classification results from a combination of different features rather than a single dominant pattern.

## 5. Discussion

The diagnosis and treatment of ocular surface tumors has undergone significant conceptual and technological changes in recent years. Traditional approaches, based mainly on clinical observation and excisional and incisional biopsy, are increasingly complemented or partially replaced by modern, non-invasive imaging tools and targeted topical therapies. Recently, artificial intelligence applications have also appeared in ophthalmology, opening up new perspectives in differential diagnosis and automated evaluation.

The three investigations presented in this dissertation reflect these parallel developments. Together, they examine the diagnostic value of new imaging techniques, explore the integration of AI-based analytical tools, and evaluate therapeutic efficacy to support a more comprehensive and precise patient care model.

Swept-source optical coherence tomography is currently one of the most widely used non-invasive examination method in the diagnosis of ocular surface tumors.

High-resolution anterior segment OCT has demonstrated reliable performance in the detection of ocular surface squamous neoplasia (OSSN), characterized by the following features: epithelial thickening and hyperreflectivity, abrupt transition zone between normal and abnormal tissue. epithelial thickening, increased hyperreflectivity, and a distinct demarcation between normal and pathological tissue.<sup>11</sup> According to our observations, the OCT characteristics of the examined ocular surface lesions were similar to those reported in the literature.<sup>12</sup>

As IVCN is a non-invasive imaging technique that allows the generation of large amounts of high-quality image data, it provides an ideal source for training and developing artificial intelligence models.<sup>13</sup> Our IVCN-based artificial intelligence model was able to identify OSSN with high accuracy. In addition, the cell-level classification results were reproducible at both the image and patient levels. The patient-specific information contained in IVCN images offers promising opportunities for personalized diagnostics and treatment monitoring in ophthalmic oncology.

From a therapeutic perspective, topical pharmacotherapy has assumed an increasingly important role in both clinical practice and research.<sup>14</sup> In our meta-analysis, we compared the efficacy and safety profiles of 5-FU, MMC, and IFN with surgical excision. Our results support that local pharmacotherapy is as effective and well-tolerated as surgical excision in terms of clinical success, recurrence rates, and complications in patients with OSSN.

Our results highlight that the diagnosis and treatment of ocular surface tumors is becoming increasingly accurate, safer, and more personalized through the integration of modern imaging technologies, artificial intelligence, and non-invasive therapeutic approaches.

## **6. Summary of novel findings**

The results of our studies demonstrate the multidimensional developmental directions of modern diagnostics and treatment of ocular surface tumors.

- By applying swept-source anterior segment OCT, we confirmed that the method is capable of visualizing the structure, depth, and extent of ocular surface lesions at high resolution, thereby possessing significant differential diagnostic value and contributing to the early recognition of premalignant and malignant lesions.
- Our artificial intelligence model based on in vivo confocal microscopy demonstrated that, even with a small dataset, it is possible to achieve highly accurate, objective, and automated identification of cell morphological alterations characteristic of ocular surface squamous neoplasia, which in the future may provide reliable support for diagnostics and therapeutic decision-making.
- The results of our systematic review and meta-analysis confirmed that the long-term efficacy and recurrence rate of topical pharmacotherapy do not fall short of the outcomes of surgical excision, thus representing a safe, non-invasive therapeutic alternative in clinical practice.

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## 8. Publications

### List of publications related to the dissertation:

1. Kozma K, Kajtár B, Orosz ZZ, Nagy B, Csutak A, Szalai E. Differential diagnostic importance of swept-source optical coherence tomography in ocular surface lesions : Swept-source OCT in ocular surface lesions. BMC Ophthalmol. 2025 May 22;25(1):307. doi: 10.1186/s12886-025-04137-1. PMID: 40405099; PMCID: PMC12100801. Impact Factor: 1.7; Q2
2. Kozma K, Jánki ZR, Bilicki V, Csutak A, Szalai E. Artificial intelligence to enhance the diagnosis of ocular surface squamous neoplasia. Sci Rep. 2025 Mar 20;15(1):9550. doi: 10.1038/s41598-025-94876-4. PMID: 40108432; PMCID: PMC11923146. Impact Factor: 3.9; Q1
3. Kozma K, Dömötör ZR, Csutak A, Szabó L, Hegyi P, Eröss B, Helyes Z, Molnár Z, Dembrowszky F, Szalai E. Topical pharmacotherapy for ocular surface squamous neoplasia: systematic review and meta-analysis. Sci Rep. 2022 Aug 20;12(1):14221. doi: 10.1038/s41598-022-18545-6. PMID: 35987957; PMCID: PMC9392743. Impact Factor: 4.6; D1

### List of conference abstracts related to the dissertation:

1. Kozma K, Kajtár B, Csutak A, Szalai E. A swept-source optikai koherencia tomográfia differenciáldiagnosztikai jelentősége a szemfelszíni elváltozásokban. Magyar Szemorvostársaság 2024. Évi Kongresszusa, Eger, 2024 június.
2. Kozma K, Jánki ZR, Bilicki V, Csutak A, Szalai E. Mesterséges intelligencia alkalmazása a szemfelszíni laphám neoplázia diagnosztikájában in vivo konfokális mikroszkóp segítségével. Magyar Szemorvostársaság 2023. Évi Kongresszusa, Bükkfürdő, 2023 június.

3. Kozma K, Jánki ZR, Bilicki V, Csutak A, Szalai E. Artificial intelligence for the diagnosis of ocular surface squamous neoplasia using in vivo confocal microscopy. ARVO Annual Meeting, USA, Louisiana, New Orleans, 2023 április
4. Kozma K, Dömötör RZ, Csutak A, Hegyi P, Dembromvszky F, Szalai E. Topikális farmakoterápia szemfelszíni laphám-neopláziák esetén: irodalmi áttekintés és meta-analízis. Magyar Szemorvostársaság 2022. Évi Kongresszusa, Bükkfürdő, 2022 június.

**List of other publications:**

1. Vajda M, Szakó L, Hegyi P, Erőss B, Görbe A, Molnár Z, Kozma K, Józsa G, Bucsí L, Schandl K. Tenodesis yields better functional results than tenotomy in long head of the biceps tendon operations-a systematic review and meta-analysis. Int Orthop. 2022 May;46(5):1037-1051. doi: 10.1007/s00264-022-05338-9. Epub 2022 Mar 7. PMID: 35254476; PMCID: PMC9001564. Impact Factor: 3.479; Q1

Cumulative impact factor of first-author publications: 10.2

Total cumulative impact factor including co-authored publications: 13.679

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