REVIEW

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Artificial intelligence for ocular oncology

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Purpose of review
The aim of this article is to provide an update on the latest applications of deep learning (DL) and classical machine learning (ML) techniques to the detection and prognostication of intraocular and ocular surface malignancies.

Recent findings
Most recent studies focused on using DL and classical ML techniques for prognostication purposes in patients with uveal melanoma (UM).

Summary
DL has emerged as the leading ML technique for prognostication in ocular oncological conditions, particularly in UM. However, the application of DL may be limited by the relatively rarity of these conditions.

Keywords
artificial intelligence, deep learning, intraocular tumor, machine learning, ocular oncology, ocular surface tumor

INTRODUCTION

Ocular oncology is a sub-specialty specialized in the diagnosis and treatment of ocular surface or intraocular tumors. Historically, the diagnosis of ocular surface and intraocular tumors were based solely on clinical examination. Ocular surface tumors have had the benefit of histopathological confirmation. Intraocular tumors however, have been managed using clinical criteria that could be inadequate. Short of enucleation, most intraocular tumors did not have appropriate histopathologic confirmation. Recently, fine needle aspiration biopsy (FNAB) of intraocular tumors has improved our diagnostic abilities for these intraocular tumors with higher accuracy and minimal complications [1]. The rise of artificial intelligence (AI) has further provided us with another tool in our armamentarium in the diagnosis and management of ocular tumors.

This review focuses on recent advances in AI applications to ocular oncological diseases. The current cutting-edge AI technique for medical image analyses is deep learning (DL), which typically requires a large amount of data for model training. Due to scarcity of oncological cases, the current review included studies that employed both classical machine learning (ML) and DL approaches.

METHODS

A systematic search of the PubMed database including the phrases 'deep learning', 'machine learning', 'artificial intelligence', 'ocular surface tumors', 'intraocular tumors' and 'oncology' was performed.

Uveal melanoma

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults [2]. The most robust predictor for patient survival is the gene expression profile (GEP) test, which can be obtained by analyzing cells aspirates from FNAB. Briefly, GEP testing was developed in the following way: molecular class assignments were made by entering the 12 delta-Ct values of each sample into the ML algorithm GIST 2.3 Support Vector Machine (SVM). The SVM was trained using a set of 28 well characterized uveal melanomas of known molecular class and clinical outcome. SVM creates a hyper-plane

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KEY POINTS

- Both classical machine learning techniques and deep learning techniques have been utilized in recently published artificial intelligence studies in ocular oncology.
- Prognostication in uveal melanoma is the most common application.
- Generative adversarial networks, few-shot learning and zero-shot learning could be used to address the scarcity of ocular tumor cases and associated image datasets.

between the training sample groups (class 1 vs. class 2), then places unknown samples on one or the other side of the hyperplane based on their GEP [3]. At 92 months, GEP class 1 patients have a survival rate of 95% and class 2 patients had a survival rate of 31% [4]. Using digital cytopathology whole slide images stained with hematoxylin–eosin for training and testing, Liu *et al.* [5] demonstrated in a pilot study with 20 patients that GEP could be predicted directly from digital cytopathology images with a point estimate of 75% accuracy on a patient level.

In a follow-up study involving a larger patient cohort by Liu *et al.* [6▪], a DL model, with a dual-attention feature extraction mechanism, was developed to directly predict GEP from digital cytopathology images. A total of 89 whole-slide images from 82 patients were included, and the data was divided into training (65 slides from 58 patients) and testing (24 slides from 24 patients) sets. The model achieved an area under the receiver operating characteristic curve (AUC) of 0.944, an accuracy of 91.7%, a sensitivity of 91.7%, and a specificity of 91.7% for GEP prediction on a slide-level analysis.

Small choroidal melanocytic tumors are a diagnostic challenge, as they could represent either as benign nevi or malignant melanomas [7]. Zabor *et al.* [8▪] developed a ML model, using lasso regression, to distinguish small choroidal melanoma (SCM) from choroidal nevus using multimodal data. A total of 123 patients with small choroidal melanocytic tumor, identified according to Collaborative Ocular Melanoma Study criteria (5.0–16.0 mm in largest basal diameter and 1.0–2.5 mm in height), were included in the training set. Presence of growth was defined as either an increase in basal dimension of at least 0.5 mm on consecutive color fundus photographs, or an increase in thickness of at least 0.3 mm on consecutive ultrasonograms. Of the 123 lesions, 30, 19, and 12 were classified as SCM based on confirmed growth, pathology and combination of growth + pathology, respectively. The remaining 62 lesions were classified as choroidal nevus due to the absence of documented growth after at least 24 months of follow-up. The presence and absence of growth was determined primarily by fundus examination, augmented by multimodal imaging if necessary. The testing set comprised of 240 patients (11 SCM and 229 choroidal nevus) from a tertiary center. The model achieved an AUC of 0.86 in the testing set in predicting growth vs. no growth in small choroidal melanocytic tumor over 24 months, using clinical variables such as; presence of subretinal fluid, tumor height, tumor distance to the optic disc and presence of orange pigment.

In a study that aimed at predicting survival in patients with UM, Chen *et al.* [9] used random forest, a classical ML technique, to construct two predictive models: whether a particular UM patient will survive more than 2 years after treatment (UM Death) and whether the tumor will metastasize within 2 years of treatment (UM Metastasis). Data regarding demographic attributes, ophthalmic examination variables (visual acuity and intraocular pressure) and tumor-specific features (largest basal diameter, thickness, pigmentation, location of the lesion, macroscopic appearance, optic nerve involvement, subretinal fluid, intraocular hemorrhage, ciliary body involvement, extraocular extension, TNM stage, initial treatment and pathology) were utilized to train the random forest models, which were tested using four-fold cross-validation. Finally, the authors investigated which features were associated with survival and the risk of metastasis, and concluded that the largest basal diameter, thickness, size, intraocular pressure and initial treatment were the parameters associated death. For predicting death, the model achieved an AUC of 0.883 and accuracy of 0.769. For predicting metastasis, the model achieved an AUC of 0.846 and an accuracy of 0.749.

Luo *et al.* [10] also developed a ML model to predict the 4-year risk of death and metastasis of UM patients, who have undergone iodine-125 plaque brachytherapy. A total of 454 patients were included to construct a model for assessing the risk of death, and 424 were included to assess the risk of metastasis. A random forest ML model was constructed for the prediction using: demographic information (age and sex), general ocular features (laterality, corrected visual acuity and intraocular pressure), clinical features of the tumor (presence of subretinal fluid, optic disk involvement, vitreous hemorrhage, ciliary body involvement, tumor thickness, tumor shape, basal diameter) on multimodal images. Using data from only a single visit, the model achieved an AUC of 0.71, accuracy of 58.5%, sensitivity of 70.5%, and specificity of 57.0% in death prediction. The model's performance improved when data from 3 visits were included: AUC of 0.88, accuracy of 83.0%, sensitivity

of 80.5% and, specificity of 83.4%. Using data from three visits, the model achieved an AUC of 0.85, accuracy of 79.5%, sensitivity of 77.1%, and specificity of 79.8% in metastasis prediction.

Donizy *et al.* [11] used classical ML models to identify predictors for metastasis and survival in patients with UM, based on routine histological and clinical measurements in cases where molecular assays were not readily available. In this study, enucleated eyes of 164 UM patients without prior treatment were included. For validation, data from 80 patients in the Tumor Cancer Genome Atlas database, which included gene expression prognostic signature (GEPS), were utilized. Three models; cox proportional hazards (CPH), random survival forest (RSF) and survival gradient boosting (SGB), were developed to identify predictors for overall survival (OS) and progression-free survival (PFS). All 3 models identified the following significant predictors for OS: age, ciliary body infiltration, mitotic rate per 1 mm^2, BAP1 status and nucleoli size. Additionally, tumor infiltrating lymphocyte and macrophage densities, largest basal diameter, nucleoli size and BAP1 status were found to be the most significant PFS predictors with all models. Although the SGB model outperformed GEPS in predicting OS and metastatic risk in time-dependent AUC, the model likely harbored selection and outcome bias, since only nucleated eyes were included. Currently, most eyes with UM are managed with local therapy, such as plaque brachytherapy or proton beam radiation, but not enucleation.

Zhang *et al.* [12] applied DL techniques and tried to predict the presence of UM based on iris color and iris images in a Chinese population. The study included 2239 nontumor and 778 UM patients. Iris regions of slit lamp photographs were automatically segmented by U-Net, and convolutional neural network (CNN) and random forest were used to classify iris color (rated on a scale of 1–5 based on the overall color of the iris from lightest to darkest). The authors did not find a correlation between iris color and presence of UM. In addition, segmented iris images were used as direct input into a CNN, which also failed to predict the presence of UM. This study confirms that there is no direct correlation between iris colors and development of UM.

Retinoblastoma

Retinoblastoma is a tumor that could benefit from more ML predictions, since biopsies of these tumors are currently contraindicated due to the risk of tumor spread outside the eye. Strijbis *et al.* [13] developed a multiview CNN (MV-CNN) for automated eye and tumor segmentation on MRI images in retinoblastoma patients. The training dataset included 40 retinoblastoma and 20 healthy eyes. The independent testing test included 11 retinoblastoma and 3 healthy eyes. The three-level pyramid MV-CNN achieved the best performance by using all MRI sequences: FIESTA, T2 and T1c. Eye and tumor volumetric interclass correlations were 0.997 and 0.996, respectively. Median [interquartile range] dice similarity coefficient for eye, sclera, vitreous, lens, retinal detachment and tumor were 0.965 [0.950–0.975], 0.847 [0.782–0.893], 0.975 [0.930–0.986], 0.909 [0.847–0.951], 0.828 [0.458–0.962], and 0.914 [0.852–0.958], respectively.

Ocular surface tumor

Yoo *et al.* [14] developed a low-shot DL model to detect conjunctival melanoma in ocular surface images. Low-shot learning is a subtype of DL that uses only very few annotated samples for model training. Using the Google search engine, the authors collected a total of 398 images from publicly available ocular surface images with the search criteria ''conjunctiva,'' ''pterygium,'' ''conjunctival nevus,'' ''conjunctival melanosis,'' ''conjunctival melanoma,'' and ''conjunctival malignant melanoma''. Various CNNs, such as GoogleNet, InceptionV3, NASNet, ResNet50, and MobileNetV2, were trained and tested. The original training dataset contained 136 conjunctival melanoma, 93 nevus or melanosis, 75 pterygium and 94 normal images. Images were divided into training ($n = 279$), validation ($n = 39$), and testing ($n = 80$) datasets. The training set was augmented using generative adversarial networks (GAN): generating 200 synthetic images with consistency GAN (CycleGAN) and 200 synthetic images with progressive growing of GAN (PGGAN). The authors created artificial anterior segment phantoms with conjunctival melanoma using a Robox 3D printer. Smartphone images of these anterior segment phantoms were then used to augment the testing set. For the detection of conjunctival melanoma, MobileNetV2 performed best (AUC: 0.976, accuracy: 96.5%), followed by NasNet (AUC: 0.972, accuracy: 95.7%), GoogleNet (AUC: 0.970, accuracy: 95.7%), ResNet-50 (AUC: 0.968, accuracy: 93.0%), and InceptionV3 (AUC: 0.954, accuracy: 92.0%). After incorporating synthetic images generated by GANs into training, the performance for all models improved, with MobileNetV2 still performing best for the detection of conjunctival melanoma (AUC: 0.983, accuracy: 97.2%). MobileNetV2 also showed an accuracy of 94.0% on smartphone images of artificial anterior segment phantoms [15].

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CONCLUSION

Although most other ophthalmology subspecialties have pivoted completely to DL, classical ML techniques are still frequently utilized in recently published ocular oncology studies. This is in part due to the relative scarcity of ocular oncological cases and high-quality images documenting such tumors. Prognostication in UM is the most common application. Analysis of digital pathology images using DL, for example to predict GEP of UM tumors, is a promising application. For future works, we anticipate more advanced DL techniques, such as generative adversarial networks, few-shot learning and zero-shot learning, will be utilized to address the scarcity of ocular oncological cases.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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