Review Article

Imaging techniques for ocular neoplasia

Amir Ahmadzadeh Amiri [1], Zahra Heidari [1,2], Reza Jafari [2], Ali Ahmadzadeh Amiri [1] and Ahmad Ahmadzadeh Amiri [1]

[1] *Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Department of Ophthalmology, Bu-Ali Sina Hospital, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran*

ABSTRACT

Background: Novel ocular imaging modalities have greatly impacted the diagnosis and management of different types of ocular neoplasia. In this narrative review, we summarize the practical features of popular and novel imaging modalities for ocular tumors.

Methods: Four databases, including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar, were searched from January 1, 2000 to August 31, 2022. Articles reporting different imaging modalities for diagnosing or monitoring treatment responses of ocular tumors were extracted using various combinations of the following keywords: ocular neoplasia, positron emission tomography or PET, single-photon emission computed tomography or SPECT, optical coherence tomography or OCT, OCT angiography or OCTA, computed tomography or CT, ultrasonography or US, ultrasound biomicroscopy or UBM, and magnetic resonance imaging or MRI.

Results: Various ocular imaging modalities had different accuracies as adjunctive tools for detecting or managing ocular tumors. Anterior ultra-high-resolution optical coherence tomography (OCT) could be used to evaluate images with < 5-μm resolution. OCT angiography provided deeper insight into retinal vascular changes associated with the malignant transformation of choroidal melanoma. OCT in children altered the diagnosis of suspicious retinoblastoma in 3% of the cases and treatment plan in 11% of the cases. While positron-emission tomography (PET)/computed tomography (CT) allowed the detection of metastatic lesions of choroidal melanoma by full-body scanning, single-photon emission CT was more sensitive compared to PET in detecting choroidal melanoma. Ultrasound biomicroscopy, with an accuracy exceeding 92.5%, could detect retinal calcification in lesions measuring 2 – 3 mm. Magnetic resonance imaging (MRI) had better contrast compared to ultrasound biomicroscopy and higher sensitivity compared to CT in detecting post-laminar optic nerve invasion. However, MRI had a lower spatial resolution compared to OCT. Further development of imaging modalities and their application in drug development would improve the treatment of ocular tumors.

Conclusions: Although diagnosing ocular tumors depend on clinical characteristics, innovations in ocular imaging have enabled early diagnosis and timely, appropriate management of ocular neoplasia, which are conducive to favorable visual outcomes and increased life expectancy. Further systematic reviews and meta-analyses of primary studies focusing on a specific imaging modality in ocular neoplasia could precisely determine the diagnostic accuracy of each imaging modality to better guide eye practitioners with efficient diagnostic or therapeutic approaches for these sight- or life-threatening entities. Imaging modalities may play a major role in drug development in the future.

KEYWORDS

neoplasia, eye neoplasm, positron emission tomography, PET scan, SPECT CT, CT SPECT scan, optical coherence tomography, ultrasonographic imaging, magnetic resonance images

Correspondence: Ahmad Ahmadzadeh Amiri, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. Email: ahmadzdh@yahoo.com. ORCID iD: https://orcid.org/0000-0002-2700-5480. Zahra Heidari, Department of Ophthalmology, Bu-Ali Sina Hospital, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. Email: zahra.heidari77@yahoo.com. ORCID iD: https://orcid.org/0000-0003-1838-9408

How to cite this article: Ahmadzadeh Amiri A, Heidari Z, Jafari R, Ahmadzadeh Amiri A, Ahmadzadeh Amiri A. Imaging techniques for ocular neoplasia. Med Hypothesis Discov Innov Optom.2022 Fall; 3(3): 86-95. https://doi.org/10.51329/mehdioptometry156

Received: 18 November 2022; Accepted: 24 December 2022

INTRODUCTION

Ocular tumors can be melanocytic, lymphoid, leukemic, fibrotic, epithelial, and lipomatous [1-5]. Recently, 3540 new cases and 350 deaths from ocular and orbital cancers have been reported in the United States [6].

Age differences exist across the types and risk factors for ocular neoplasia. Children are predisposed to retinoblastoma (RB) and rhabdomyosarcoma, while adults can develop uveal melanoma (UM) and ocular lymphoma [7, 8]. Risk factors associated with RB include genetic or individual predispositions [7, 9]. Risk factors associated with UM include congenital eye melanocytosis, light eye color, white ethnicity, and exposure to ultraviolet rays [10-12].

Understanding intraocular tumors and their ocular complications are factors determining their response to treatment and practical management [13-15]. Appropriate diagnostic tools are essential for the early detection and management of ocular cancer. Although biopsy with histological examination is the gold standard for confirming a tumor, advanced noninvasive imaging techniques have equal reliability in diagnosing ocular tumors [7, 8].

Recent advances in ocular imaging have greatly influenced the diagnosis and treatment of both anterior and posterior segment eye diseases [16, 17]. In addition to pre-treatment diagnosis [18], imaging modalities are vital for post-treatment monitoring of ocular tumors and evaluation of response to chemotherapy management [19, 20]. Moreover, novel ocular imaging approaches may help the development of appropriate treatment modalities for intraocular tumors [21].

In this narrative review, we summarize novel imaging modalities commonly used for diagnosing or managing ocular tumors (Figure 1), including choroidal melanoma, RB, and anterior and posterior segment tumors, or for drug development, based on the literature published since 2000. We summarize the clinical presentation of the most common ocular tumors diagnosed using different imaging modalities and discuss the advantages and disadvantages of each modality. In addition, we briefly explain various pharmacokinetic studies on eye tissues using imaging modalities to elucidate its potential use in drug development.

METHODS

The literature was searched from the official home pages of PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar from January 1, 2000 to August 31, 2022 using various combinations of the following keywords: ocular neoplasia, positron emission tomography or PET, single-photon emission computed tomography or SPECT, optical coherence tomography or OCT, optical coherence tomography angiography or OCTA, computed tomography or CT, ultrasonography or US, ultrasound biomicroscopy or UBM, and magnetic resonance imaging or MRI. The eligibility criterion was detection or management of ocular tumors using the imaging modality with high accuracy. After reviewing the title, abstract, and full text, articles that met the eligibility criteria were evaluated by two independent reviewers (A.A. and Z.H.), and disagreements were resolved in consultation with a third reviewer (R.J.). Studies on nontumoral eye lesions were excluded. Finally, relevant articles on imaging modalities for detecting or managing ocular neoplasia were selected, and their full text was reviewed.

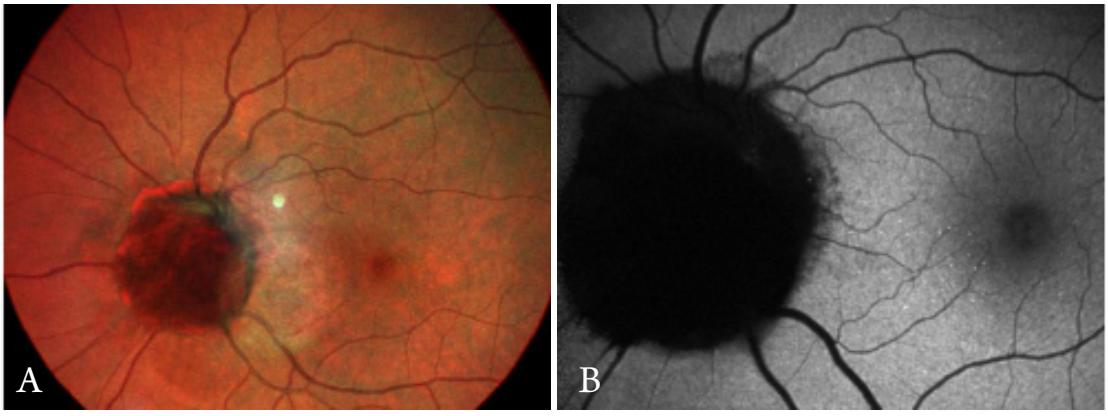

Figure 1. (A) Color fundus photograph (Topcon TRC50LX, Topcon, Tokyo, Japan) showing left eye optic disc melanocytoma as a highly pigmented black-brownish lesion involving most of the optic disc and adjacent retina. (B) The fundus autofluorescence (Heidelberg Engineering, Heidelberg, Germany) shows hypofluorescence of the lesion corresponding to the pigmented mass and adjacent retina.

RESULTS

The initial search yielded 136 articles, of which relevant articles were selected, and their practical points were summarized. RB in children and UM in adults were the most common intraocular malignant tumors [22-24]. On histological assessment, RB had calcification in over 95% of cases [22], and ocular calcification in children younger than 3 years indicated RB. Approximately 5% of all melanomas in adults were UMs, and 5% of UMs were located in the iris [23, 24].

Another common adult tumor was ocular lymphoma, often associated with non-Hodgkin's lymphoma. It was found inside the eye, orbit, and adnexa. Orbital lymphoma was the most common orbital cancer in adults, and 5% of the patients with lymphoma were at risk for secondary orbital lymphoma [25].

Table 1 summarizes the available imaging modalities as adjunctive tools for the assessment of ocular tumors along with their advantages and disadvantages. The imaging modalities are discussed in detail below.

DISCUSSION

Positron emission tomography (PET)

PET uses the high glucose uptake in tumor cells to retrieve information about the location, size, and shape of the tumor and thereby distinguish between cancerous and normal structures. A radioactive form of glucose, such as fluoro-2-deoxyglucose18 (FDG), is injected intravenously and accumulates in the tumoral tissue [26, 27]. PET is then performed to obtain detailed information about tumor cells [26]. PET alone is sensitive for the detection of metastatic lesions in orbital squamous cell carcinoma [26].

However, the sensitivity of PET is inferior to that of magnetic resonance imaging (MRI) in detecting metastatic liver lesions in newly diagnosed UM [36]. FDG-based glucose metabolism is not sensitive for the diagnosis of choroidal melanoma or liver metastases from UM [26, 37, 38]. FDG absorption with false-positive results for nonmalignant cell detection has been reported. Inflammatory, infectious, or traumatic processes can cause false-positive results [39]. However, the importance of PET/computed tomography (CT) in staging pediatric cancers, such as rhabdomyosarcoma, has been reported [40]. PET can be used for staging choroidal melanoma based on the glucose uptake. CT can reduce the false-positive rate [41], and combined CT and PET improves the diagnostic accuracy [40, 41].

Table 1. Advantages and disadvantages of various imaging modalities used for ocular tumors

Imaging Modality	Advantage	Disadvantage
PET-CT Scan	It offers the possibility of scanning the whole body to diagnose metastatic lesions and diagnosis of medium to large UMs [26].	The amount of glucose uptake is unknown for tumors, and tumors with a low metabolic rate cannot be diagnosed. Radiopharmaceuticals are used, thereby increasing the risk of secondary cancer [27].
SPECT	It is more sensitive compared to PET in diagnosing UMs [28].	Its diagnostic accuracy depends on timely imaging, and it is recommended to be performed after 48 h of an intravenous ^{123}I-IMP injection. In addition, radiopharmaceuticals are used, thereby increasing the risk of secondary cancer [29].
AS-OCT	It is suitable to diagnose tumors of the anterior segment of the eye and is a safe diagnostic tool without using radiopharmaceuticals [30].	It is unsuitable for pigmented tumors because of a less penetrating power and for tumors of the posterior segment of the eye. It fails to detect metastatic lesions, unlike PET or SPECT [31].
UBM	It has a superior ability for penetration compared to AS-OCT in diagnosing anterior segment tumors, and diagnosing RB in the fetus is affordable, efficient, and available [32].	It cannot provide epithelial detail as seen on UHR-OCT or confocal microscopy [33].
MRI	It is a radiation-free imaging modality and promising in diagnosing fetal RB. It is better for soft tissue imaging compared to CT and ultrasound. It has a wide application in the diagnosis of RB and UM, particularly metastatic ones [34].	The image of calcified tissue is poor compared to CT. Motion artifact affects image resolution. It is expensive and difficult to access [35].

Abbreviation: PET-CT Scan, positron emission tomography-computed tomography; UM, uveal melanoma; SPECT, single photon emission computed tomography; ^{123}I-IMP, N-isopropyl-*p*-[^{123}I]iodoamphetamine; AS-OCT, anterior segment optical coherence tomography; UBM, ultrasound biomicroscopy; RB, retinoblastoma; UHR-OCT, ultrahigh-resolution OCT; MRI, magnetic resonance imaging.

Reddy et al. [42] showed that both PET/CT scanners could detect medium and large tumors. Finger et al. [43] proposed PET/CT as a noninvasive marker for metastatic choroidal melanoma. Calcagni et al. [44] showed that differences in glucose metabolism could be used to distinguish between different types of low- and high-risk UM cancer cells. In a study by McConnell et al. [45], PET/CT showed 100% sensitivity for the diagnosis of choroidal melanoma with loss of chromosome number 3. This is a useful screening tool with low false-positive results to detect liver metastasis in patients with UM [41].

In addition, radiopharmaceuticals used in PET induce a risk of radiation-induced tumors. Huang et al. [27] reported that the risk of cancer development after PET/CT decreased as the age at exposure increased. Children with RB gene mutations are susceptible to secondary neoplasia due to exposure to ionizing radiation; therefore, PET/CT is not recommended in children [46].

Single-photon emission CT (SPECT)

SPECT is the three-dimensional (3D) counterpart of planar radioisotope imaging that uses radionuclides and records the emission of gamma rays from different angles with a nuclear camera [28, 29]. Goto et al. [28] described the use of N-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) for diagnosing UM with atypical clinical manifestations. The basic principle of this technique is the positive correlation between the accumulation of ^{123}I-IMP and the amount of melanin [28].

In a comparative study of PET and SPECT for diagnosing malignant UM, Abe et al. [29] found that SPECT was more sensitive 24 h after intravenous ^{123}I-IMP administration and that imaging after the intravenous ^{123}I-IMP injection was effective for differentiating malignant melanoma from non-malignant nevus only 48 h after the injection. Yamazaki et al. [47] showed that SPECT images integrated with CT images, which is a standardized uptake value method evaluated at a 6-h time point, can predict ^{123}I-IMP uptake at a 24-h time point and is more predictive for detecting choroidal melanoma compared to the conventional count-based uptake index method [47].

In a meta-analysis, Liu et al. [48] compared ^{18}F-fluoride PET/CT and technetium-99-methylene diphosphonate bone scan (BS) in detecting bone metastases and found that the sensitivity was higher when the results were equivocally positive for BS (sensitivity, 96%; specificity, 93%), but the specificity was higher when equivocal results were reported as negative for BS (specificity, 95%; sensitivity, 93%) [48].

Optical coherence tomography (OCT)

OCT was developed based on optical coherence interference to measure the frequency of the returning beams from the eye and compare it with the reference light. The time and spectral domains are two types of OCT with high resolutions [30, 49]. Ultra-high-resolution (UHR) OCT is an advanced OCT technique that reveals abnormal features of ocular neoplasia [30, 50, 51]. High-resolution enhanced-depth OCT is a promising modality for the precise measurement of posteriorly located choroidal nevi [52].

Ocular neoplasia, such as surface squamous, conjunctival lesions (pigmented and non-pigmented), choroidal nevi, epithelioma, melanocytoma (Figure 1), and other forms of ocular neoplasia, can be diagnosed using OCT [30, 50-52]. Pavlin et al. [32] reported that OCT could help evaluate anterior segment tumors, particularly small hypopigmented iris tumors, with large infiltrating iris hypopigmented tumors not being imaged as well as small ones. A retrospective study by Bianciotto et al. [50] reported that OCT is only suitable for treating hypopigmented tumors. OCT can detect 18-μm lesions of high quality [50].

Nanji et al. [31] reported 71 patients with ocular surface squamous neoplasia (OSSN), lymphoma, and pigmented conjunctival lesions diagnosed using UHR-OCT with high accuracy. In addition, UHR-OCT is a useful method for differentiating thick tumoral lesions and squamous hyperactivity of the ocular surface from other ocular surface lesions, such as keratoconjunctivitis, pterygium, and Salzmann's nodular degeneration [53-55]. Intraoperative UHR-OCT aids in better visualization of tumor margins and guides surgical approaches for these lesions [56].

Lozanco Garcia et al. [57] reported that UHR-OCT has a 100% sensitivity and specificity for diagnosing OSSN from pterygium, with a cutoff point of 141 μm for epithelial thickness. Subclinical disease detected on UHR-OCT in patients with a definite clinical resolution of OSSN can help clinicians prevent disease progression or recurrence [58]. Hyperreflective bands in subepithelial lesions on UHR-OCT are related to paracellular infiltration based on histopathology and confirmed as conjunctival lymphoma [59]. The ability of UHR-OCT to image conjunctival lymphoma lesions can be restricted by the substantial thickness of the lesion, leading to lower structural details in deeper subepithelial tissues [60].

Recently, OCT angiography (OCTA) has revealed distinctive vascular patterns in OSSN lesions. The density of blood vessels in the body of OSSN tumors is higher than that in the underlying conjunctiva and subepithelial

tissue [61]. In a study by Brouwer et al. [62], anterior-segment OCTA showed tortuous vascular patterns in conjunctival melanoma differing from the vascular patterns seen in primary acquired melanosis (PAM) of the conjunctiva and normal conjunctiva; conjunctival nevi also have internal cystic structures relative to PAM lesions and conjunctival melanoma [62].

OCTA is used to profile the vasculature of the retina or optic disc [61], and its measurements can be helpful for the early detection of radiation retinopathy or optic neuropathy after brachytherapy in the eyes with UM through quantitative biomarkers [63]. OCTA can measure ischemia-related retinal quantitative capillary changes related to the visual acuity and radiation dose, and the development of radiation-induced retinal toxicity related to radiation may be predicted with this approach in the future [63, 64].

Ultrasound biomicroscopy (UBM)

Ultrasound waves with different frequencies were used in UBM. A major limitation of UBM is the use of the liquid immersion technique, which may not be possible in all patients [16]. Ultrasound waves are superior to light waves and enable better visualization of ocular tumors with a transition through large and highly pigmented tumors [34]. It is a useful modality to detect ocular tumors and their locations [32] and calcification with an accuracy exceeding 92.5% [65].

Ultrasonography (US) can be used for screening and predicting RB in fetus and for amniocentesis [66, 67]. In one study, US was used at 33 weeks of pregnancy to detect RB in the macular region of one eye [68]. It is easier and more cost-effective for diagnosing fetal RB compared to MRI [32] (Table 1). In addition, invasive tumors present as blunting of the anterior chamber, invasive tissue in the anterior chamber angle, ciliary body, or thickness of uvea on UBM 50 MHz [69, 70]. Meel et al. [33] found that latent intraocular invasion of OSSN could be diagnosed with UBM in patients with risk factors, such as nodular or ulcerative tumor morphology, tumor thickness of > 5 mm in height, or history of immunosuppressant use or surgical intervention [33, 69].

UBM is necessary for non-specific clinical manifestations of UM [71]. UM is a neoplasm that develops from the choroidal melanocytes, ciliary body, and iris in 90%, 7%, and 3% of the cases, respectively [72]. Molecular abnormalities and mutations have been identified in UM [73]. A choroidal nevus can progress to melanoma with age, which is a major problem in Europe and the United States because of population aging [74].

Magnetic Resonance Imaging (MRI)

Radiation-free MRI uses powerful static magnets for imaging. Various components of MRI have made it the surrogate gold-standard modality to evaluate the orbit and brain in RB after the gold-standard modality histopathology [75]. Studies have identified different aspects of RB and UM diagnoses using MRI. Schueler et al. [76] showed the use of high-resolution MRI for RB with hyperintense and hypointense signals in T1- and T2-weighted images relative to the vitreous, respectively; however, they had limited value in visualizing the prelaminar and postlaminar optic nerves. MRI has a weak ability to detect calcification caused by RB compared to CT; calcium appears hypointense on MRI [76].

Lemke et al. [77] showed a sensitivity of 91.7% and specificity of 88.9% for detecting a specific amount of intraocular calcification with MRI. However, small motion artifacts may impair the quality of the MRI image; even advanced MRI technology, such as UHR trans-3D turbo spin echo T2-weighted MRI, is prone to motion artifacts despite noise removal [78]. Therefore, various strategies have been developed to overcome the effects of eye movement on MRI [79, 80].

Bilateral posterior pole lesions can be identified at 35 weeks of pregnancy with MRI image resolution without affecting fetal movement [81]. The contrast resolution of MRI is better than that of UBM, and MRI has a higher sensitivity than CT for detecting post-laminar invasion in the optic nerve of eyes with RB [82]. MRI shows a sensitivity of 95% in the diagnosis of post-laminar invasion [82].

MRI enables the diagnosis of UM and can help with treatment planning using proton radiation. Daftari et al. [35] investigated the possible use of T2-weighted rapid rotation 3D MRI images in treatment planning for intraocular malignancy and found that MRI was excellent for demonstrating intraocular tumor volumes and provided additional information regarding the tumor shape. Direct MRI volumetric measurements showed a high degree of accuracy for tumor volume in patients with UM [35]. Optic nerve sheath meningioma (ONSM) is a rare, benign tumor of the optic nerve. MRI is preferred for diagnosing ONSM [83]. Despite the presence of pneumosinus dilatans, optic canal enlargement, and nerve sheath calcification of ONSM on CT, MRI is considered the gold-standard diagnostic modality [84].

Although MRI has a lower spatial resolution compared to OCT, it allows for simultaneous ocular and orbital imaging [85]. It is highly accurate in diagnosing metastatic liver lesions in the early detection of UM.

It helps formulate an appropriate treatment plan and provides information about the anatomical relationships of the tumor before brachytherapy, proton-beam therapy, and stereotactic radiotherapy [86]. With continuous advancements in MRI technology, radiofrequency coil design, and further optimization of MR sequences, MRI could become a superior imaging approach for diagnosing UM [87] or ocular tumors.

Imaging technology in drug development

Ophthalmic CT or MRI with tumor volume measurements is an example of assessing the effectiveness of newly developed chemotherapeutic drugs used to treat ocular tumors [88, 89]. Similarly, imaging-based biomarkers can provide areas of greater immunization, safety, and molecular efficacy of medicine. Bergstrom et al. [88] proposed PET as a potential tool for determining the pharmacokinetics and release of new molecules during drug production. By using a radioactive ligand, changes in the receptor can be easily detected on PET to determine the pharmacokinetics of the new drug [89]. FDG-PET is used to monitor FDG uptake before and after bevacizumab treatment of rectal tumors [90].

Conventional pharmacokinetic techniques for analyzing the ocular distribution of drugs are invasive and rely on animal models. Human studies are generally performed concurrently with ocular surgery, such as vitrectomy [91], which can be alternatives to overcome these shortcomings. Successfully using micro-dialysis in determining the intratumoral pharmacokinetics of chemotherapy drugs, such as carboplatin and 5-fluorouracil, in RB has been reported [92]. Fernandez-Ferreiro et al. [93] used a PET/CT scanner to determine the clearance of three radiopharmaceutical molecules in the vitreous. A recent study demonstrated the use of PET as a potential noninvasive tool for conducting pharmacokinetic studies on ophthalmic drugs. SPECT/CT has also been used as a noninvasive tool for monitoring ocular drug distribution [94].

In another study on the binding of melanin to labeled ^{123}I-IMP, the distribution and elimination of this molecule in albino and pigmented rats were studied using SPECT/CT as a tool for non-invasive control of drug pharmacokinetics [95]. Dynamic contrast-enhanced MRI has been used to study the spatial and temporal distributions of drugs and the uniformity and permeability of the blood–retinal barrier [96-98]. Despite advantages of MRI in the development of ophthalmic drug delivery, it has limitations compared to conventional pharmacokinetics, including low sensitivity, selective monitoring using radiopharmaceutical contrast, different relaxation times of protons in tissues, such as vitreous or aqueous humor, and high cost [99]. Studies are required to confirm the efficacy of integrating different imaging modalities to understand the kinetics, dynamics, and development of ocular drugs for managing vision-threatening tumors.

In this narrative review, we outlined the trend in innovations in ocular imaging techniques over the past two decades that has enabled early diagnosis and timely management of ocular neoplasias to achieve favorable visual outcomes and increase life expectancy. However, this review is limited by the lack of a comprehensive literature search, and some influential articles might have been overlooked. In addition, we presented an overview of various ocular imaging modalities but failed to examine the detailed practical points or diagnostic accuracy of each modality. Further systematic reviews and meta-analyses of primary studies focusing on a specific imaging modality in ocular neoplasia could precisely determine the diagnostic accuracy of each imaging modality to better guide eye practitioners toward efficient diagnostic or therapeutic approaches in these sight or life-threatening entities. Finally, despite significant advances in imaging techniques, they are considered adjunctive tools for detecting or managing ocular tumors and cannot substitute thorough clinical examinations or careful regular follow-ups. For both anterior- and posterior-segment tumors, the importance of regular anterior-segment slit-photo or fundus photography for monitoring and documenting baseline features and tumor progression cannot be overstated.

CONCLUSIONS

Various ocular tumors can be accurately detected using various imaging modalities. The advantages and disadvantages of imaging modalities should be considered based on the nature of the tumor. Although MRI is expensive, it is safe and has a wider scope for diagnosing various types of ocular tumors. OCT and US are superior to other techniques, particularly for diagnosing anterior-segment tumors. Despite caution regarding the radiation risk and higher cost associated with using PET/CT and SPECT, these are useful for whole-body scanning to detect metastatic lesions. In multipurpose diagnoses using different approaches, the advantages and disadvantages of each modality can be neutralized and show better diagnostic possibilities compared to a single imaging method. Imaging modalities may play a major role in drug development in the future. Further development of imaging modalities with higher resolution would solve the current challenges in ocular tumor detection, and their application in drug development would improve the treatment of ocular tumors.

ETHICAL DECLARATIONS

Ethical approval: Not required.
Conflict of interests: None

FUNDING

None.

ACKNOWLEDGMENTS

The corresponding author (Ahmad Ahmadzadeh Amiri) has a paternal relationship with Amir Ahmadzadeh Amiri and Ali Ahmadzadeh Amiri, with all having valid authorship contributions.

REFERENCES

1. Pe'er J. Pathology of eyelid tumors. Indian J Ophthalmol. 2016;64(3):177-90. doi: 10.4103/0301-4738.181752 pmid: 27146927
2. Shields CL, Demirci H, Karatza E, Shields JA. Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. Ophthalmology. 2004;111(9):1747-54. doi: 10.1016/j.ophtha.2004.02.013 pmid: 15350332
3. Othman IS. Ocular surface tumors. Oman J Ophthalmol. 2009;2(1):3-14. doi: 10.4103/0974-620X.48415 pmid: 21234217
4. Shields CL, Alset AE, Boal NS, Casey MG, Knapp AN, Sugarman JA, et al. Conjunctival Tumors in 5002 Cases. Comparative Analysis of Benign Versus Malignant Counterparts. The 2016 James D. Allen Lecture. Am J Ophthalmol. 2017;173:106-133. doi: 10.1016/j.ajo.2016.09.034 pmid: 27725148
5. Elshazly LH. A clinicopathologic study of excised conjunctival lesions. Middle East Afr J Ophthalmol. 2011;18(1):48-54. doi: 10.4103/0974-9233.75886 pmid: 21572734
6. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. doi: 10.3322/caac.21708 pmid: 35020204
7. Chintagumpala M, Chevez-Barrios P, Paysse EA, Plon SE, Hurwitz R. Retinoblastoma: review of current management. Oncologist. 2007;12(10):1237-46. doi: 10.1634/theoncologist.12-10-1237 pmid: 17962617
8. Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol. 2013;6(7):1230-44. pmid: 23826405
9. Pandey AN. Retinoblastoma: An overview. Saudi J Ophthalmol. 2014;28(4):310-5. doi: 10.1016/j.sjopt.2013.11.001 pmid: 25473349
10. Houtzagers LE, Wierenga APA, Ruys AAM, Luyten GPM, Jager MJ. Iris Colour and the Risk of Developing Uveal Melanoma. Int J Mol Sci. 2020;21(19):7172. doi: 10.3390/ijms21197172 pmid: 32998469
11. Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken JF, Giles GG, et al. Artificial ultraviolet radiation and ocular melanoma in Australia. Int J Cancer. 2004;112(5):896-900. doi: 10.1002/ijc.20476 pmid: 15386378
12. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association between host susceptibility factors and uveal melanoma: a meta-analysis. Arch Ophthalmol. 2006;124(1):54-60. doi: 10.1001/archopht.124.1.54 pmid: 16401785
13. Lingam G. Options for management of intra ocular tumors. Indian J Ophthalmol. 2015;63(3):204-10. doi: 10.4103/0301-4738.156913 pmid: 25971164
14. Tarlan B, Kıratlı H. Uveal Melanoma: Current Trends in Diagnosis and Management. Turk J Ophthalmol. 2016;46(3):123-137. doi: 10.4274/tjo.37431 pmid: 27800275
15. Konstantinidis L, Rospond-Kubiak I, Zeolite I, Heimann H, Groenewald C, Coupland SE, et al. Management of patients with uveal metastases at the Liverpool Ocular Oncology Centre. Br J Ophthalmol. 2014;98(1):92-8. doi: 10.1136/bjophthalmol-2013-303519 pmid: 24169654
16. Konstantopoulos A, Hossain P, Anderson DF. Recent advances in ophthalmic anterior segment imaging: a new era for ophthalmic diagnosis? Br J Ophthalmol. 2007;91(4):551-7. doi: 10.1136/bjo.2006.103408 pmid: 17372341
17. Heimann H, Jmor F, Damato B. Imaging of retinal and choroidal vascular tumours. Eye (Lond). 2013;27(2):208-16. doi: 10.1038/eye.2012.251 pmid: 23196648
18. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020;68(11):2356-2365. doi: 10.4103/ijo.IJO_721_20 pmid: 33120616
19. Chen S, Ji X, Liu M, Xia Z, Zheng H, Yin Q, et al. The value of MRI in evaluating the efficacy and complications with the treatment of intra-arterial chemotherapy for retinoblastoma. Oncotarget. 2017;8(24):38413-38425. doi: 10.18632/oncotarget.16423 pmid: 28415600
20. Foti PV, Travali M, Farina R, Palmucci S, Spatola C, Liardo RLE, et al. Diagnostic methods and therapeutic options of uveal melanoma with emphasis on MR imaging-Part II: treatment indications and complications. Insights Imaging. 2021;12(1):67. doi: 10.1186/s13244-021-01001-w pmid: 34085131
21. Afarid M, Mahmoodi S, Baghban R. Recent achievements in nano-based technologies for ocular disease diagnosis and treatment, review and update. J Nanobiotechnology. 2022;20(1):361. doi: 10.1186/s12951-022-01567-7 pmid: 35918688
22. Aerts I, Lumbroso-Le Rouic L, Gauthier-Villars M, Brisse H, Doz F, Desjardins L. Retinoblastoma. Orphanet J Rare Dis. 2006;1:31. doi: 10.1186/1750-1172-1-31 pmid: 16934146
23. Harbour JW. The genetics of uveal melanoma: an emerging framework for targeted therapy. Pigment Cell Melanoma Res. 2012;25(2):171-81. doi: 10.1111/j.1755-148X.2012.00979.x pmid: 22268848
24. Ramaiya KJ, Harbour JW. Current management of uveal melanoma. Expert Rev Ophthalmol. 2007;2(6):939-46. doi: 10.1586/17469899.2.6.939

25. Metser U, Goor O, Lerman H, Naparstek E, Even-Sapir E. PET-CT of extranodal lymphoma. AJR Am J Roentgenol. 2004 Jun;182(6):1579-86. doi: 10.2214/ajr.182.6.1821579 pmid: 15150013
26. Spraul CW, Lang GE, Lang GK. Value of positron emission tomography in the diagnosis of malignant ocular tumors. Ophthalmologica. 2001;215(3):163-8. doi: 10.1159/000050851 pmid: 11340384
27. Huang B, Law MW, Khong PL. Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. Radiology. 2009;251(1):166-74. doi: 10.1148/radiol.2511081300 pmid: 19251940
28. Goto H. Clinical efficacy of 123I-IMP SPECT for the diagnosis of malignant uveal melanoma. Int J Clin Oncol. 2004;9(2):74-8. doi: 10.1007/s10147-003-0380-2 pmid: 15108037
29. Abe K, Sasaki M, Koga H, Kaneko K, Sawamoto H, Yoshikawa H, et al. Clinical role of 123I-IMP SPECT for the differential diagnosis of ocular malignant melanoma: a time-course analysis. Nucl Med Commun. 2007;28(7):567-73. doi: 10.1097/MNM.0b013e328194f221 pmid: 17538399
30. Thomas BJ, Galor A, Nanji AA, El Sayyad F, Wang J, Dubovy SR, et al. Ultra high-resolution anterior segment optical coherence tomography in the diagnosis and management of ocular surface squamous neoplasia. Ocul Surf. 2014;12(1):46-58. doi: 10.1016/j.jtos.2013.11.001 pmid: 24439046
31. Nanji AA, Sayyad FE, Galor A, Dubovy S, Karp CL. High-Resolution Optical Coherence Tomography as an Adjunctive Tool in the Diagnosis of Corneal and Conjunctival Pathology. Ocul Surf. 2015;13(3):226-35. doi: 10.1016/j.jtos.2015.02.001 pmid: 26045235
32. Pavlin CJ, Vásquez LM, Lee R, Simpson ER, Ahmed II. Anterior segment optical coherence tomography and ultrasound biomicroscopy in the imaging of anterior segment tumors. Am J Ophthalmol. 2009;147(2):214-219.e2. doi: 10.1016/j.ajo.2008.08.023 pmid: 18930449
33. Meel R, Dhiman R, Sen S, Kashyap S, Tandon R, Vanathi M. Ocular Surface Squamous Neoplasia with Intraocular Extension: Clinical and Ultrasound Biomicroscopic Findings. Ocul Oncol Pathol. 2019;5(2):122-127. doi: 10.1159/000490251 pmid: 30976591
34. Feygin T, Leahey AM. Retinoblastoma: Advanced Imaging, Clinical Approach. Journal of Pediatric Neuroradiology. 2015;4(04):082-96. doi: 10.1055/s-0036-1584135
35. Daftari Ik, Aghaian E, O'Brien JM, Dillon W, Phillips TL. 3D MRI-based tumor delineation of ocular melanoma and its comparison with conventional techniques. Med Phys. 2005;32(11):3355-62. doi: 10.1118/1.2068927 pmid: 16372413
36. Aide N, Iravani A, Prigent K, Kottler D, Alipour R, Hicks RJ. PET/CT variants and pitfalls in malignant melanoma. Cancer Imaging. 2022;22(1):3. doi: 10.1186/s40644-021-00440-4 pmid: 34983677
37. Strobel K, Bode B, Dummer R, Veit-Haibach P, Fischer DR, Imhof L, et al. Limited value of 18F-FDG PET/CT and S-100B tumour marker in the detection of liver metastases from uveal melanoma compared to liver metastases from cutaneous melanoma. Eur J Nucl Med Mol Imaging. 2009;36(11):1774-82. doi: 10.1007/s00259-009-1175-0 pmid: 19495748
38. Hui KH, Pfeiffer ML, Esmaeli B. Value of positron emission tomography/computed tomography in diagnosis and staging of primary ocular and orbital tumors. Saudi J Ophthalmol. 2012;26(4):365-71. doi: 10.1016/j.sjopt.2012.08.008 pmid: 23961021
39. Patel P, Finger PT. Whole-body 18F FDG positron emission tomography/computed tomography evaluation of patients with uveal metastasis. Am J Ophthalmol. 2012;153(4):661-8. doi: 10.1016/j.ajo.2011.09.028 pmid: 22264690
40. Colleran GC, Kwatra N, Oberg L, Grant FD, Drubach L, Callahan MJ, et al. How we read pediatric PET/CT: indications and strategies for image acquisition, interpretation and reporting. Cancer Imaging. 2017;17(1):28. doi: 10.1186/s40644-017-0130-8 pmid: 29116015
41. Finger PT, Kurli M, Reddy S, Tena LB, Pavlick AC. Whole body PET/CT for initial staging of choroidal melanoma. Br J Ophthalmol. 2005;89(10):1270-4. doi: 10.1136/bjo.2005.069823 pmid: 16170114
42. Reddy S, Kurli M, Tena LB, Finger PT. PET/CT imaging: detection of choroidal melanoma. Br J Ophthalmol. 2005;89(10):1265-9. doi: 10.1136/bjo.2005.066399 pmid: 16170113
43. Finger PT, Chin K, Iacob CE. 18-Fluorine-labelled 2-deoxy-2-fluoro-D-glucose positron emission tomography/computed tomography standardised uptake values: a non-invasive biomarker for the risk of metastasis from choroidal melanoma. Br J Ophthalmol. 2006;90(10):1263-6. doi: 10.1136/bjo.2006.097949 pmid: 16837539
44. Calcagni ML, Mattoli MV, Blasi MA, Petrone G, Sammarco MG, Indovina L, et al. A prospective analysis of ^{18}F-FDG PET/CT in patients with uveal melanoma: comparison between metabolic rate of glucose (MRglu) and standardized uptake value (SUV) and correlations with histopathological features. Eur J Nucl Med Mol Imaging. 2013;40(11):1682-91. doi: 10.1007/s00259-013-2488-6 pmid: 23824464
45. McCannel TA, Reddy S, Burgess BL, Auerbach M. Association of positive dual-modality positron emission tomography/computed tomography imaging of primary choroidal melanoma with chromosome 3 loss and tumor size. Retina. 2010;30(1):146-51. doi: 10.1097/IAE.0b013e3181b32f36 pmid: 20010323
46. Aerts I, Pacquement H, Doz F, Mosseri V, Desjardins L, Sastre X, et al. Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institut Curie. Eur J Cancer. 2004;40(10):1522-9. doi: 10.1016/j.ejca.2004.03.023 pmid: 15196536
47. Yamazaki K, Nishii R, Maeda T, Makishima H, Kasuya G, Chang T, et al. Assessment of SPECT-CT fusion images and semi-quantitative evaluation using SUV in 123I-IMP SPECT in patients with choroidal melanoma. Ann Nucl Med. 2020;34(11):864-872. doi: 10.1007/s12149-020-01517-z pmid: 32902695
48. Liu Y, Sheng J, Dong Z, Xu Y, Huang Q, Pan D, et al. The diagnostic performance of 18F-fluoride PET/CT in bone metastases detection: a meta-analysis. Clin Radiol. 2019;74(3):196-206. doi: 10.1016/j.crad.2018.12.011 pmid: 30648535
49. Simpson T, Fonn D. Optical coherence tomography of the anterior segment. Ocul Surf. 2008;6(3):117-27. doi: 10.1016/s1542-0124(12)70280-x pmid: 18781258
50. Bianciotto C, Shields CL, Guzman JM, Romanelli-Gobbi M, Mazzuca D Jr, Green WR, et al. Assessment of anterior segment tumors with ultrasound biomicroscopy versus anterior segment optical coherence tomography in 200 cases. Ophthalmology. 2011;118(7):1297-302. doi: 10.1016/j.ophtha.2010.11.011 pmid: 21377736
51. Oellers P, Karp CL. Management of pigmented conjunctival lesions. Ocul Surf. 2012;10(4):251-63. doi: 10.1016/j.jtos.2012.08.002 pmid: 23084146

52. Shah SU, Kaliki S, Shields CL, Ferenczy SR, Harmon SA, Shields JA. Enhanced depth imaging optical coherence tomography of choroidal nevus in 104 cases. Ophthalmology. 2012;119(5):1066-72. doi: 10.1016/j.ophtha.2011.11.001 pmid: 22297027
53. Hurmeric V, Yoo SH, Galor A, Canto AP, Wang J. Atypical presentation of Salzmann nodular degeneration diagnosed with ultra-high-resolution optical coherence tomography. Ophthalmic Surg Lasers Imaging. 2011;42 Online:e122-5. doi: 10.3928/15428877-20111201-05 pmid: 22150601
54. Kieval JZ, Karp CL, Abou Shousha M, Galor A, Hoffman RA, Dubovy SR, et al. Ultra-high resolution optical coherence tomography for differentiation of ocular surface squamous neoplasia and pterygia. Ophthalmology. 2012;119(3):481-6. doi: 10.1016/j.ophtha.2011.08.028 pmid: 22154538
55. Vajzovic LM, Karp CL, Haft P, Shousha MA, Dubovy SR, Hurmeric V, et al. Ultra high-resolution anterior segment optical coherence tomography in the evaluation of anterior corneal dystrophies and degenerations. Ophthalmology. 2011;118(7):1291-6. doi: 10.1016/j.ophtha.2010.12.015 pmid: 21420175
56. Karp CL, Mercado C, Venkateswaran N, Ruggeri M, Galor A, Garcia A, et al. Use of High-Resolution Optical Coherence Tomography in the Surgical Management of Ocular Surface Squamous Neoplasia: A Pilot Study. Am J Ophthalmol. 2019;206:17-31. doi: 10.1016/j.ajo.2019.05.017 pmid: 31163136
57. Lozano García I, Romero Caballero MD, Sellés Navarro I. High resolution anterior segment optical coherence tomography for differential diagnosis between corneo-conjunctival intraepithelial neoplasia and pterygium. Arch Soc Esp Oftalmol (Engl Ed). 2020;95(3):108-113. English, Spanish. doi: 10.1016/j.oftal.2020.01.002 pmid: 32007344
58. Tran AQ, Venkateswaran N, Galor A, Karp CL. Utility of high-resolution anterior segment optical coherence tomography in the diagnosis and management of sub-clinical ocular surface squamous neoplasia. Eye Vis (Lond). 2019;6:27. doi: 10.1186/s40662-019-0152-3 pmid: 31463333
59. Venkateswaran N, Mercado C, Tran AQ, Garcia A, Diaz PFM, Dubovy SR, et al. The use of high resolution anterior segment optical coherence tomography for the characterization of conjunctival lymphoma, conjunctival amyloidosis and benign reactive lymphoid hyperplasia. Eye Vis (Lond). 2019;6:17. doi: 10.1186/s40662-019-0143-4 pmid: 31236423
60. Tanenbaum RE, Galor A, Dubovy SR, Karp CL. Classification, diagnosis, and management of conjunctival lymphoma. Eye Vis (Lond). 2019;6:22. doi: 10.1186/s40662-019-0146-1 pmid: 31372366
61. Liu Z, Karp CL, Galor A, Al Bayyat GJ, Jiang H, Wang J. Role of optical coherence tomography angiography in the characterization of vascular network patterns of ocular surface squamous neoplasia. Ocul Surf. 2020;18(4):926-935. doi: 10.1016/j.jtos.2020.03.009 pmid: 32344147
62. Brouwer NJ, Marinkovic M, Bleeker JC, Luyten GPM, Jager MJ. Anterior Segment OCTA of Melanocytic Lesions of the Conjunctiva and Iris. Am J Ophthalmol. 2021;222:137-147. doi: 10.1016/j.ajo.2020.09.009 pmid: 32926848
63. de Carlo TE, Mieler WF. Automated quantitative OCTA measurements of uveal melanoma-treated eyes with and without radiation retinopathy after I-125 plaque therapy and of nonirradiated fellow eyes. Eye (Lond). 2021;35(3):769-776. doi: 10.1038/s41433-020-01237-8 pmid: 33223531
64. Skalet AH, Liu L, Binder C, Miller AK, Crilly R, Hung AY, et al. Longitudinal Detection of Radiation-Induced Peripapillary and Macular Retinal Capillary Ischemia Using OCT Angiography. Ophthalmol Retina. 2020;4(3):320-326. doi: 10.1016/j.oret.2019.10.001 pmid: 31757690
65. Roth DB, Scott IU, Murray TG, Kaiser PK, Feuer WJ, Hughes JR, et al. Echography of retinoblastoma: histopathologic correlation and serial evaluation after globe-conserving radiotherapy or chemotherapy. J Pediatr Ophthalmol Strabismus. 2001;38(3):136-43. doi: 10.3928/0191-3913-20010501-06 pmid: 11386645
66. Paquette LB, Miller D, Jackson HA, Lee T, Randolph L, Murphree AL, et al. In utero detection of retinoblastoma with fetal magnetic resonance and ultrasound: initial experience. AJP Rep. 2012;2(1):55-62. doi: 10.1055/s-0032-1316465 pmid: 23946908
67. Toi A, Sutherland J, Gallie B, Gardiner J, Sermer M. Evaluation of the fetus at risk for retinoblastoma: what is the role of prenatal ultrasound? Ultrasound in Medicine and Biology. 2003;29(5):S137. doi: 10.1016/S0301-5629(03)00562-3
68. Stathopoulos C, Say EAT, Shields CL. Prenatal ultrasonographic detection and prenatal (prior to birth) management of hereditary retinoblastoma. Graefes Arch Clin Exp Ophthalmol. 2018;256(4):861-862. doi: 10.1007/s00417-017-3841-4 pmid: 29151167
69. Kaliki S, Jajapuram SD, Maniar A, Taneja S, Mishra DK. Ocular surface squamous neoplasia with intraocular tumour extension: a study of 23 patients. Eye (Lond). 2020;34(2):319-326. doi: 10.1038/s41433-019-0503-2 pmid: 31292522
70. He M, Wang D, Jiang Y. Overview of Ultrasound Biomicroscopy. J Curr Glaucoma Pract. 2012;6(1):25-53. doi: 10.5005/jp-journals-10008-1105 pmid: 27990069
71. Li X, Wang L, Zhang L, Tang F, Wei X. Application of Multimodal and Molecular Imaging Techniques in the Detection of Choroidal Melanomas. Front Oncol. 2021;10:617868. doi: 10.3389/fonc.2020.617868 pmid: 33634026
72. Souto EB, Zielinska A, Luis M, Carbone C, Martins-Gomes C, Souto SB, et al. Uveal melanoma: physiopathology and new in situ-specific therapies. Cancer Chemother Pharmacol. 2019;84(1):15-32. doi: 10.1007/s00280-019-03860-z pmid: 31079217
73. Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH, et al. Uveal melanoma. Nat Rev Dis Primers. 2020;6(1):24. doi: 10.1038/s41572-020-0158-0. Erratum in: Nat Rev Dis Primers. 2022;8(1):4. pmid: 32273508
74. Shields CL, Dalvin LA, Ancona-Lezama D, Yu MD, Di Nicola M, Williams BK Jr, et al. Choroidal Nevus Imaging Features in 3,806 Cases and Risk Factors for Transformation into Melanoma in 2,355 Cases: The 2020 Taylor R. Smith and Victor T. Curtin Lecture. Retina. 2019;39(10):1840-1851. doi: 10.1097/IAE.0000000000002440 pmid: 30608349
75. Sirin S, de Jong MC, de Graaf P, Brisse HJ, Galluzzi P, Maeder P, et al; European Retinoblastoma Imaging Collaboration. High-Resolution Magnetic Resonance Imaging Can Reliably Detect Orbital Tumor Recurrence after Enucleation in Children with Retinoblastoma. Ophthalmology. 2016;123(3):635-45. doi: 10.1016/j.ophtha.2015.10.054 pmid: 26692298
76. Schueler AO, Hosten N, Bechrakis NE, Lemke AJ, Foerster P, Felix R, et al. High resolution magnetic resonance imaging of retinoblastoma. Br J Ophthalmol. 2003;87(3):330-5. doi: 10.1136/bjo.87.3.330 pmid: 12598449
77. Lemke AJ, Kazi I, Mergner U, Foerster PI, Heimann H, Bechrakis N, et al. Retinoblastoma - MR appearance using a surface coil in comparison with histopathological results. Eur Radiol. 2007;17(1):49-60. doi: 10.1007/s00330-006-0197-2 pmid: 16636801
78. Simon EM, McCaffery S, Rowley HA, Fischbein NJ, Shimikawa A, O'Brien JM. High-resolution 3D T2-weighted fast spin echo: new

applications in the orbit. Neuroradiology. 2003;45(7):489-92. doi: 10.1007/s00234-003-0954-8 pmid: 12802545
79. Niendorf T, Beenakker JM, Langner S, Erb-Eigner K, Bach Cuadra M, Beller E, et al. Ophthalmic Magnetic Resonance Imaging: Where Are We (Heading To)? Curr Eye Res. 2021;46(9):1251-1270. doi: 10.1080/02713683.2021.1874021 pmid: 33535828
80. Fanea L, Fagan AJ. Review: magnetic resonance imaging techniques in ophthalmology. Mol Vis. 2012;18:2538-60. pmid: 23112569
81. Staffieri SE, McGillivray G, Elder JE, Bristowe A, Cole S, McKenzie JD, et al. Managing fetuses at high risk of retinoblastoma: lesion detection on screening MRI. Prenat Diagn. 2015;35(2):174-8. doi: 10.1002/pd.4514 pmid: 25284592
82. Brisse HJ, Guesmi M, Aerts I, Sastre-Garau X, Savignoni A, Lumbroso-Le Rouic L, et al. Relevance of CT and MRI in retinoblastoma for the diagnosis of postlaminar invasion with normal-size optic nerve: a retrospective study of 150 patients with histological comparison. Pediatr Radiol. 2007;37(7):649-56. doi: 10.1007/s00247-007-0491-4 pmid: 17479257
83. Douglas VP, Douglas KAA, Cestari DM. Optic nerve sheath meningioma. Curr Opin Ophthalmol. 2020;31(6):455-461. doi: 10.1097/ICU.0000000000000700 pmid: 33009076
84. Shapey J, Sabin HI, Danesh-Meyer HV, Kaye AH. Diagnosis and management of optic nerve sheath meningiomas. J Clin Neurosci. 2013;20(8):1045-56. doi: 10.1016/j.jocn.2013.03.008 pmid: 23809100
85. Lindner T, Langner S, Falke K, Walter U, Krüger PC, Pohlmann A, et al. Anatomic and pathological characterization of choroidal melanoma using multimodal imaging: what is practical, what is needed? Melanoma Res. 2015;25(3):252-8. doi: 10.1097/CMR.0000000000000156 pmid: 25831415
86. Ferreira TA, Grech Fonk L, Jaarsma-Coes MG, van Haren GGR, Marinkovic M, Beenakker JM. MRI of Uveal Melanoma. Cancers (Basel). 2019;11(3):377. doi: 10.3390/cancers11030377 pmid: 30884881
87. Foti PV, Travali M, Farina R, Palmucci S, Spatola C, Raffaele L, et al. Diagnostic methods and therapeutic options of uveal melanoma with emphasis on MR imaging-Part I: MR imaging with pathologic correlation and technical considerations. Insights Imaging. 2021;12(1):66. doi: 10.1186/s13244-021-01000-x pmid: 34080069
88. Bergström M, Grahnén A, Långström B. Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development. Eur J Clin Pharmacol. 2003;59(5-6):357-66. doi: 10.1007/s00228-003-0643-x pmid: 12937873
89. Pien HH, Fischman AJ, Thrall JH, Sorensen AG. Using imaging biomarkers to accelerate drug development and clinical trials. Drug Discov Today. 2005;10(4):259-66. doi: 10.1016/S1359-6446(04)03334-3 pmid: 15708744
90. Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med. 2004;10(2):145-7. doi: 10.1038/nm988. Erratum in: Nat Med. 2004;10(6):649. pmid: 14745444
91. Agrahari V, Mandal A, Agrahari V, Trinh HM, Joseph M, Ray A, et al. A comprehensive insight on ocular pharmacokinetics. Drug Deliv Transl Res. 2016;6(6):735-754. doi: 10.1007/s13346-016-0339-2 pmid: 27798766
92. Azeredo FJ, Dalla Costa T, Derendorf H. Role of microdialysis in pharmacokinetics and pharmacodynamics: current status and future directions. Clin Pharmacokinet. 2014;53(3):205-212. doi: 10.1007/s40262-014-0131-8 pmid: 24452811
93. Fernández-Ferreiro A, Luaces-Rodríguez A, Aguiar P, Pardo-Montero J, González-Barcia M, García-Varela L, et al. Preclinical PET Study of Intravitreal Injections. Invest Ophthalmol Vis Sci. 2017;58(7):2843-2851. doi: 10.1167/iovs.17-21812 pmid: 28570736
94. Subrizi A, Toropainen E, Ramsay E, Airaksinen AJ, Kaarniranta K, Urtti A. Oxidative stress protection by exogenous delivery of rhHsp70 chaperone to the retinal pigment epithelium (RPE), a possible therapeutic strategy against RPE degeneration. Pharm Res. 2015;32(1):211-21. doi: 10.1007/s11095-014-1456-6 pmid: 25030185
95. Rimpelä AK, Schmitt M, Latonen S, Hagström M, Antopolsky M, Manzanares JA, et al. Drug Distribution to Retinal Pigment Epithelium: Studies on Melanin Binding, Cellular Kinetics, and Single Photon Emission Computed Tomography/Computed Tomography Imaging. Mol Pharm. 2016;13(9):2977-86. doi: 10.1021/acs.molpharmaceut.5b00787 pmid: 26741026
96. Berkowitz BA, Roberts R, Luan H, Peysakhov J, Mao X, Thomas KA. Dynamic contrast-enhanced MRI measurements of passive permeability through blood retinal barrier in diabetic rats. Invest Ophthalmol Vis Sci. 2004;45(7):2391-8. doi: 10.1167/iovs.03-1381 pmid: 15223822
97. Kim SH, Csaky KG, Wang NS, Lutz RJ. Drug elimination kinetics following subconjunctival injection using dynamic contrast-enhanced magnetic resonance imaging. Pharm Res. 2008;25(3):512-20. doi: 10.1007/s11095-007-9408-z pmid: 17674155
98. Jelescu IO, Leppert IR, Narayanan S, Araújo D, Arnold DL, Pike GB. Dual-temporal resolution dynamic contrast-enhanced MRI protocol for blood-brain barrier permeability measurement in enhancing multiple sclerosis lesions. J Magn Reson Imaging. 2011;33(6):1291-300. doi: 10.1002/jmri.22565 pmid: 21590997
99. Li SK, Lizak MJ, Jeong EK. MRI in ocular drug delivery. NMR Biomed. 2008;21(9):941-56. doi: 10.1002/nbm.1230 pmid: 18186077