In Asians, polypoidal choroidal vasculopathy (PCV) is becoming more widely recognized as a significant cause of exudative maculopathy. The previous set of Indian guidelines on the management of PCV were published in 2018, with a literature search updated up to November 2015. As the treatment of PCV evolves, retinal physicians must constantly modify their current practice. The current guidelines are based on the most up-to-date information on PCV and are an update to the previous set of guidelines. These guidelines were developed by a panel of Indian retinal experts under the aegis of the Vitreoretinal Society of India (VRSI), based on a comprehensive search and assessment of literature up to September 2021. The final guidelines i) provide the updated nomenclature in PCV; ii) discusses the newer diagnostic imaging features of PCV, especially in the absence of indocyanine green angiography (ICGA); and iii) recommends the best possible therapeutic approach in the management of PCV, including the choice of anti-vascular endothelial growth factor (anti-VEGF) agents, treatment regimen, and the role of switching between the anti-VEGF agents. In the face of non-availability of photodynamic therapy (PDT) in India, we constructed practical recommendations on anti-VEGF monotherapy in PCV. The current updated recommendations would provide a broader framework to the treating retinal physician for the diagnosis and management of PCV for optimal therapeutic outcomes.

**Key words:** Indocyanine green angiography, optical coherence tomography, polypoidal choroidal vasculopathy, vitreoretinal society of India

In 2018, a panel of Indian retinal specialists, now known as the Indian Polypoidal Choroidal Vasculopathy Panel (IPCVP) generated the first consensus recommendations for the diagnosis, treatment, and follow-up schedule of polypoidal choroidal vasculopathy (PCV).[1] These recommendations were designed, published, and available for free download for practitioners globally. While the guidelines were based upon the literature existing up to 2015, considerable developments have taken place in the management of PCV since then.

In 2021, the Asia-Pacific Ocular Imaging Society (APOIS) PCV Workgroup proposed the consensus nomenclature and terminologies of optical coherence tomography (OCT) biomarkers for the detection of PCV.[2] They recommended updating the terminology of “polyp” to “polypoidal lesion (PL)” and replacing the term “branching vascular network (BVN)” with “branching neovascular network (BNN)” to accurately represent the neovascular character of the vascular network inside the PCV complex.[3] They also put forth a combination of OCT-based major (sub-retinal pigment epithelial [sub-RPE] ring-like lesion, en face OCT complex RPE elevation, and sharp-peaked pigment epithelial detachment [PED]) and minor (double-layer sign [DLS], thick choroid with dilated Haller’s layer, and complex or multi-lobular PED) criteria for non-indocyanine green angiography (non-ICGA)–based diagnosis of PCV.[2] For determining the lesion area, the workgroup noted that a combination of OCT with en face near-infrared (NIR) reflectance imaging covered 100% of the PL area and 91%±12% of the branching neovascular network (BNN) area when compared to the ICGA treatment spot.[3]

**Department of Clinical Research, Chaithanya Eye Hospital, Trivandrum, 1Vitreoretinal Society of India (VRSI) General Secretary, Vitreoretinal Society of India, 2Department of Vitreoretina, Giridhar Eye Institute, Kochi, Kerala, 3Department of Vitreoretinal Services, Sri Bhagwan Mahavir Vitreoretinal Services, Medical Research Foundation, Chennai, Tamil Nadu, India, 4Department of Vitreoretina, Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates, 5Vitreoretinal Society of India (VRSI) President, Vitreoretinal Society of India, 2Vitreoretinal Society of India (VRSI) Convenor Scientific Committee, Vitreoretinal Society of India, India**

**Correspondence to:** Dr. Raja Narayanan, Room 603C, LV Prasad Eye Institute, Banjara Hills, Hyderabad, Telangana - 500 034, India.

E-mail: narayanan@lvpei.org

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Newer anti-vascular endothelial growth factor (anti-VEGF) molecules such as brolucizumab have become available, while the availability of photodynamic therapy (PDT), considered the gold standard in PCV management, is challenging and has been currently unprocurable in India since 2020. There has been a considerable increase in publications evaluating the role of anti-VEGF monotherapy with different molecules and evaluating diverse treatment regimens for PCV. The volume of literature with varying levels of evidence can be challenging to construe and form a meaningful interpretation by the treating physician. For these reasons, the Vitreoretinal Society of India (VRSI) convened the IPCVP to conduct a systematic literature review and provide updated consensus recommendations for the diagnosis, treatment, and follow-up schedule of PCV.

Methods
A systematic review was initiated in September 2021. Electronic databases including PubMed and Medline were methodically searched for studies evaluating the diagnosis and management of PCV using the following search terminologies: “PCV”, “PCV and clinical features”, “PCV and classification”, “PCV and diagnosis” or “imaging” or “indocyanine green angiography (ICGA)” or “fundus fluorescein angiography (FFA)” or “optical coherence tomography (OCT)”, “PCV and PDT”, “PCV and thermal laser (TL)”, and “PCV and bevacizumab” or “ranibizumab” or “aflibercept” or “brolucizumab” or “anti-VEGF”. All articles up to 9 September 2021 were manually and meticulously screened by the panel, and relevant literature was selected to formulate the consensus guidelines. Review articles and case reports with ≤5 patients were excluded.

Consensus Evidence-Based Guidelines

When to suspect the presence of PCV on clinical evaluation?

Summary of the 2018 guidelines (Recommendation 1)[1]

Suspect PCV in the presence of one of the following classical clinical features [Fig. 1]:
1. Reddish-orange subretinal nodules
2. Serosanguineous maculopathy
3. A disproportionate amount of exudation as compared to the size of the lesion

Updated 2021 Recommendation 1

There are no proposed major changes to the 2018 recommendations. A minor revision includes the deletion of the “Non-responsiveness to anti-VEGF therapy” criteria for suspecting PCV.

Imaging in polypoidal choroidal vasculopathy

Is indocyanine green mandatory for the diagnosis of PCV?

Summary of the 2018 guidelines (Recommendation 2)[1]
ICGA is considered to be the current gold standard for the detection and evaluation of PCV.

Updated 2021 Recommendation 2
ICGA is a preferred imaging modality in the diagnosis of PCV [Fig. 2]. However, in the absence of ICGA, a combination of three OCT features: sub-RPE ring-like lesion, en face OCT complex RPE elevation, and sharp-peaked pigment PED can be utilized with considerable accuracy for the diagnosis of PCV. Additional features such as a hyperreflective shallow irregular PED (double-layer sign) and presence of tall-peaked PED with primarily subretinal fluid (SRF) with/without intraretinal fluid (IRF) are also indicative of PCV on spectral domain OCT (SD-OCT). ICGA is mandatory for clinical trials on PCV, but may not be essential in real-world management, especially considering the primary treatment with anti-VEGF injections in macular PCV.

Basis for the updated recommendations
ICGA remains an invasive procedure requiring specific imaging equipment which is not readily accessible to retinal physicians. On OCT, a combination of features including sub-RPE ring-like lesion, en face OCT complex RPE elevation, and sharp-peaked pigment PED achieved an area under the receiver operating characteristic curve of 0.90, with a sensitivity of 0.75, specificity of 0.91, positive predictive value (PPV) of 0.93, and negative predictive value (NPV) of 0.68 in 110 eyes, with PCV evaluated by the APOIS PCV Workgroup.[2] Since these guidelines are established by the
APOIS, these can be applicable in India, given the importance of regional variations in retinal manifestations based on ethnicity and geography. Figs. 3 and 4 illustrate the classic SD-OCT features of PCV.

When should we perform ICGA?

Summary of the 2018 guidelines (Recommendation 3)

Classic clinical features of PCV described above with or without characteristic notched/peaked PED on OCT is an indication to perform an ICGA.

Updated 2021 Recommendation 3

In case of poor response to anti-VEGF, or in hemorrhagic PCV where extrafoveal polyps can be lasered, ICGA is recommended.

How to define “Polyp” and “Abnormal Vascular Network” on ICGA? Which phases of ICGA are critical for diagnosing PCV?

Updated 2021 Recommendation 4

No major changes to the 2018 recommendations pertaining to the ICGA phases and ICGA-based classification of PCV. The term BNN encompasses the previously described terminologies of the abnormal vascular network associated with the PCV complex, namely the BVN, abnormal vascular network (AVN), and the interconnecting channel (IC).[3]

How to decide on the extent of the lesion on ICGA?

Summary of the 2018 guidelines (Recommendation 5)[1]:

The total lesion area of PCV is the total area including all polyps and AVN on ICGA.

Updated 2021 Recommendation 5

The total lesion area of PCV is the total area including all the polypoidal lesions and the BNN on ICGA. In the absence of ICGA, a combination of near-infrared (NIR) reflectance image and OCT can be utilized to determine the treatment area (as validated by the APOIS PCV Workgroup).[3] The importance of measuring the polypoidal area becomes applicable only for PDT-based treatment. For an OCT-based treatment, the relevance of the lesion area is probably only to understand the lesion involvement to educate the patient and prognosticate the treatment.

Is Fundus fluorescein angiography necessary in PCV?

Summary of the 2018 guidelines (Recommendation 6)[1];

Fundus fluorescein angiography (FFA) should be performed in all patients of PCV at the initial examination to identify the presence or absence of leakage from the AVN, which plays a role in prognosticating the disease outcome.

Updated 2021 Recommendation 6

Performing an FFA is not mandatory in the management of PCV.

What are the characteristic features of PCV on OCT?

Summary of the 2018 guidelines (Recommendation 7)[1];

Based on OCT, PCV can be suspected if there is the presence of any one of the following features:
1. Thumb-like polyp (TLP)/Sharp-peaked PED: Denotes polyp
2. Tomographic notch in PED: Signifies the polypoidal lesion at the margin of the PED
3. Hyporeflective lumen surrounded by a hyperreflective ring attached to the undersurface of RPE
4. Double-layer sign (DLS): Presence of two hyperreflective lines on SD-OCT representing shallow irregular RPE elevation and Bruch’s membrane, signifying AVN.

The presence of normal/increased choroidal thickness (pachychoroid) on enhanced-depth imaging OCT (EDI-OCT) provides supportive evidence of PCV and can be used to differentiate it from age-related macular degeneration (AMD), in which the choroid is usually thin.

Updated 2021 Recommendation 7

There are no major changes to the 2018 recommendations. Few minor revisions and additions have been included:
1. The sharp-peaked PED is defined as a PED having a sharp vertical inclination of >70° and a height:base-to-width ratio >1.
2. The tomographic notched PED has been re-labelled as complex or multi-lobular PED.
3. Presence of thick choroid based on the age and refractive error/axial length, a subfoveal choroidal thickness (SFCT) of ≥300 µm, and/or presence of focal dilated Haller’s layer vessels with overlying choriocapillaris attenuation.
4. Presence of complex RPE elevation on en face OCT.
comprising of the hyperreflective BNN which connects multiple PEDs.

5. Presence of fluid which is chiefly subretinal, with/without intraretinal involvement.

**Basis for the updated recommendations**

The APOIS PCV Workgroup assessed these additional OCT biomarkers for their diagnostic value in PCV and then validated in 80 PCV eyes. In literature, different imaging studies on PCV have utilized varied OCT machines, including the SD-OCT and the swept source OCT (SS-OCT). The APOIS PCV Workgroup utilized the SD-OCT for formulating the diagnostic criteria of PCV. Although utilizing the SS-OCT may provide better quality images, the use of these expensive imaging modalities may be beyond the purview of many retina specialists in a developing country such as India. Thus, the panel recommends to utilize either the SD-OCT or the SS-OCT, whichever is accessible to the treating retinologist, for imaging the PCV. The screening protocol should involve macular volume scan comprising of 25 scans over 6 × 6 mm area centered on the fovea. Since macular location is most commonly seen in PCV, this scanning protocol should suffice in a majority of the cases. However, the panel recommends to alter the scanning loci based on the area of interest as seen on clinical examination and the rendered fundus imaging. It is important to highlight that peripheral PCV are difficult to scan; hence clinical examination is crucial for diagnosing these cases. Furthermore, the peripheral location of these exudative lesions eliminates the diagnosis of neovascular AMD (nAMD) while still being a characteristic feature of PCV.

**Is it possible to differentiate between PCV and neovascular AMD on OCT?**

*Summary of the 2018 guidelines (Recommendation 8)*

By identifying classical features of PCV on OCT such as tall-peaked PED, notched PED, DLS, and TLP, it may be possible to suspect PCV and differentiate it from nAMD to a large extent. Nonetheless, ICGA remains the gold standard in diagnosing PCV and should be performed if available.

**Updated 2021 Recommendation 8**

There are no major changes to the 2018 recommendations. The additional OCT features including sub-RPE ring-like lesion, en face OCT complex RPE elevation, and thick choroid with dilated Haller’s layer are also important imaging biomarkers for the diagnosis of PCV. On multimodal imaging, a combination of three features, namely sharp-peaked PED and sub-RPE ring-like structure on OCT and the presence of an orange nodule on clinical fundus photograph (CFP) are very sensitive for accurate diagnosis of PCV.

**Basis for the updated recommendations**

The additional OCT features were validated by the APOIS PCV Workgroup for their diagnostic significance in PCV. Furthermore, they also evaluated the usefulness of an orange nodule on CFP in differentiating between PCV and nAMD eyes. They noted that a combination of three features, including sharp-peaked PED, sub-RPE ring-like structure on OCT, and orange nodule on CFP showed good agreement with ICGA for PCV diagnosis.

**How to decide whether to treat/observe PCV? If treatment is essential, how do we decide on the area of treatment?**

*Summary of the 2018 guidelines (Recommendation 9)*

The treatment of PCV is primarily based on its location, and whether it is active or inactive. The entire PCV lesion including the polyp and AVN should be treated.

**Updated 2021 Recommendation 9**

There are no major changes to the 2018 recommendations. The entire PCV lesion including the PL and BNN should be treated.
Basis for the updated recommendations
The terminologies of “polyp” and “AVN” have been updated to “polypoidal lesions” and “BNN” as discussed earlier.[2]

How do we define disease activity?
Summary of the 2018 guidelines (Recommendation 10)[3]
PCV can be considered active in the presence of one of the following features:
1. Intraretinal/subretinal fluid
2. Sub-RPE/subretinal hemorrhage
3. Vision loss ≥5 ETDRS letters.

Leakage on FFA can be considered as a corroborative feature in defining the disease activity.

Updated 2021 Recommendation 10
There are no proposed changes to the 2018 recommendations pertaining to the SD-OCT biomarkers and visual acuity parameters. Since FFA is no longer mandatory in the management of PCV, its utility for monitoring disease activity is redundant.

When to treat PCV?
Summary of the 2018 guidelines (Recommendation 11)[3];
1. Active symptomatic PCV: Treat
2. Active asymptomatic PCV: Can consider treatment based on the discretion
3. Inactive PCV: Observe.

Updated 2021 Recommendation 11
There are no proposed changes to the 2018 recommendations.

Treatment of subfoveal and juxtafoveal polypoidal choroidal vasculopathy
When is PDT indicated in PCV? Is a combination therapy with an anti-VEGF agent essential?
Summary of the 2018 guidelines (Recommendation 12)[3]
Active subfoveal and juxtafoveal PCV should be treated with full-fluence PDT with three loading doses of anti-VEGF injections.

Updated 2021 Recommendation 12
Due to the non-availability of PDT, anti-VEGF monotherapy is the definite choice for the management of active subfoveal and juxtafoveal PCV.

What is the role of anti-VEGF agents in the management of PCV, both as a primary modality of treatment and in the management of residual/recurrent PCV?
Summary of the 2018 guidelines (Recommendation 13)[3]
If initially the extent of the lesion is not clearly defined on ICGA due to the presence of blocked fluorescence secondary to hemorrhage, it is advisable to initiate anti-VEGF monotherapy alone. Once the hemorrhage clears, ICGA + FFA should be performed and if PCV is confirmed, combination therapy with PDT and anti-VEGF agent should be done. Anti-VEGF monotherapy can also be considered in peripapillary PCV. In exceptional situations, such as lack of access to PDT and resource-constrained countries, there may be an unavoidable situation of treating with anti-VEGF monotherapy. However, there is a strong possibility that there may be an incomplete resolution of polyps, and the number of injections required would be more than what may be required when PDT is combined with anti-VEGF therapy.

Updated 2021 Recommendation 13
Anti-VEGF monotherapy can be considered in patients with PCV especially due to the unavailability of PDT. In hemorrhagic PCV, anti-VEGF monotherapy can be initiated. Once the hemorrhage clears and the diagnosis of PCV is confirmed, treatment with anti-VEGF monotherapy can be continued, especially with agents such as aflibercept which have shown non-inferior results to combination therapy with PDT.

Summary of the 2018 guidelines (Recommendation 14)[3]
Indications for initiation with anti-VEGF monotherapy:
1. Small submacular hemorrhage associated with PCV (<4DD)
2. Thin submacular hemorrhage associated with PCV (<500 μm)
3. Polyp extent not clearly defined by ICG
4. Peripapillary PCV.

Updated 2021 Recommendation 14
In addition to the 2018 recommendations, anti-VEGF monotherapy with aflibercept is also an effective alternative to combination therapy with PDT, both as a primary treatment and for residual/recurrence, for the management of PCV.

Basis for the updated Recommendations 12, 13, and 14
Results from multiple studies including the Afiblercept in Polypoidal Choroidal Vasculopathy (PLANET) study have validated the non-inferiority of intravitreal aflibercept monotherapy to intravitreal aflibercept with rescue PDT.[5] Moreover, the use of PDT has many drawbacks: 1) Vision-threatening complications such as hemorrhage (subretinal, vitreous, suprachoroidal), RPE rips, and choroidal ischemia and atrophy; 2) Inability to treat PCV lesions which are widely distributed or in the peripapillary region, or associated with significant hemorrhage/large PED at baseline; and 3) Repeated PDT treatment, which is usually needed due to the high recurrence rate of PCV lesions, heightens the risk of choroidal atrophy in the long run.[6–13] In a subgroup of Japanese PCV patients from the PLANET study, the authors concluded that intravitreal anti-VEGF monotherapy was effective in the treatment of PCV whilst rescue PDT did not provide any additional advantages.[14] Thus, using the available evidence and given the difficulties in procuring PDT, the panel recommends starting the patient on anti-VEGF therapy with aflibercept as a primary treatment modality for PCV and also for recurrences/residual disease. Figs. 5 and 6 illustrate two cases treated with anti-VEGF monotherapy.

Of all the anti-VEGF agents available today, which one should be the agent of choice?
Summary of the 2018 guidelines (Recommendation 15)[3]
Ranibizumab is considered the preferred anti-VEGF agent based on level 1 evidence. Although no level 1 evidence exists for aflibercept use till now, it can also be considered as a primary anti-VEGF agent or in patients refractory to ranibizumab based on the physician’s discretion.

Updated 2021 Recommendation 15
Based on level 1 evidence, aflibercept should be the preferred anti-VEGF agent for PCV.[5] Although no level 1 evidence exists comparing aflibercept and ranibizumab, initiating the treatment with aflibercept can be considered due to its stronger binding affinity to VEGF, additional activity against the placental growth factor (PGF), and a longer half-life.
which provides an opportunity for q8/q12 weekly dosing after the initial loading regimen. Brolucizumab therapy can be considered for PCV eyes refractory to both aflibercept and ranibizumab, given the limited evidence and higher rates of intraocular inflammation.[4]

Basis for the updated recommendations
The majority of the landmark trials including the EVEREST, LAPTOP, and FUSIJAN have demonstrated the efficacy of ranibizumab in PCV management.[16–23] The 24-month results of the EVEREST-2 study showed ranibizumab monotherapy to be inferior to combination therapy with PDT in terms of polyp regression rate of (26.7% vs 56.6%), best corrected visual acuity (BCVA) letter gain (5.5 vs 9.6), and the median number of injections needed (12 vs 6).[15] As against this, the PLANET study established the non-inferiority of intravitreal aflibercept therapy to intravitreal aflibercept with rescue PDT.[13] For the patients who required rescue PDT, the authors did not note any additional visual benefit.[15] Although a direct comparison between the PLANET and EVEREST study is limited due to different study designs, the EVEREST study essentially proposes ranibizumab in combination with PDT for achieving optimal outcomes in PCV while the PLANET study indicates intravitreal aflibercept monotherapy to be on par with intravitreal aflibercept with rescue PDT in PCV management.[5,15] Cho H J compared the efficacy of ranibizumab and aflibercept in 98 treatment-naïve patients with PCV.[16] At 12 months, both agents achieved similar visual outcomes but the polyp regression rate was significantly more with aflibercept than with ranibizumab (39.5% vs 21.6%).[16] Many workers have also demonstrated the efficacy of aflibercept in PCV refractory to ranibizumab therapy.[19–23] The higher affinity to VEGF and additive effect on PGF can account for the beneficial outcomes of aflibercept in refractory cases.[19–23] Moreover, its longer durability makes it ideal for a treat-and-extend (T&E) regimen with q8/q12 dosing, thereby reducing the treatment burden in the long run.[24] Brolucizumab is another similar agent with a longer duration of action.[42] Although a couple of studies have shown its good efficacy in eyes with PCV, the rates of intraocular inflammatory episodes were considerably high in both of them (15.4% and 19%).[5,26] Moreover, any studies are absent comparing it with PDT. Thus, its role in PCV needs further evaluation due to very limited evidence in the literature. In the subgroup analysis of PCV eyes in the HAWK trial, brolucizumab was better than aflibercept in anatomical outcomes while having similar visual gains.[4] Considering these factors, the panel recommends aflibercept as the preferred anti-VEGF agent for PCV, while brolucizumab can be considered for refractory cases with a cautionary note pertaining to intraocular inflammation.

What should be our follow-up protocol for patients? When should ICGA + FFA be repeated after initiating therapy?
Summary of the 2018 guidelines (Recommendation 16)[1]
ICGA + FFA should be repeated after three months to analyze disease activity. If quiescent, ICGA + FFA should be repeated after 6 months and 12 months, respectively. BCVA and OCT should be performed at all follow-up visits. For incomplete regression of polyps, re-treatment with full-fluence PDT with intravitreal injection of anti-VEGF should be performed. Half-fluence PDT may also be considered if the BCVA is ≥20/40. If FFA/ICGA shows no polyp, but the persistence of leaking AVN, monotherapy with anti-VEGF should be performed.

Updated 2021 Recommendation 16
ICGA can be repeated after six months, or as needed based on the disease recurrence, although it is not mandatory. Likewise, performing an FFA is a non-requisite. Serial OCT is an important tool in following up the patients. Since PDT is not available, consider switching to aflibercept if the patient has already received three-loading doses of bevacizumab or ranibizumab with poor response.

How do we recognize and manage recurrent PCV?
Summary of the 2018 guidelines (Recommendation 17)[1]
At any of the follow-up visits, if there is a drop in BCVA, or appearance of hemorrhage, or exudation seen clinically, or presence of fluid (subretinal/intraretinal) on OCT, ICGA + FFA should be repeated. For recurrence of polyps seen on FFA/ICGA, retreatment with full-fluence PDT with intravitreal injection of anti-VEGF should be performed. Reduced-fluence PDT may also be considered if the BCVA is ≥20/40. If FFA/ICGA shows no polyp but the persistence of leaking AVN, monotherapy with anti-VEGF should be executed.

Updated 2021 Recommendation 17
There are no major changes to the 2018 recommendations. In the absence of ICGA, OCT can be utilized to evaluate for biomarkers of disease activity such as subretinal or intraretinal fluid (SRF/IRF). For incomplete regression or recurrence of PL or BNN on ICGA and/or presence of OCT biomarkers of activity, the patient can be given anti-VEGF monotherapy. Use of the T&E regimen with longer-acting agents such as aflibercept is recommended to reduce the treatment burden and follow-up visits of the patient.

Basis for the updated Recommendations 16 and 17
ICGA is an invasive procedure that is not readily available.[1] With advances in imaging and recognition of newer OCT biomarkers for accurate diagnosis of PCV, as discussed previously under recommendation 2, a more practical approach is to follow-up the patients with OCT after initiating the treatment. PCV is known to have a high recurrence rate, ranging from 40%–78.6% at three years.[27] The SD-OCT features such as SRF and IRF are important for early recognition of disease recurrence, similar to nAMD.[1,13] Although the FLUID study demonstrated comparable visual acuity outcomes with the “relaxed” strategy (tolerating fluid up to 200 µ) and the “strict fluid-free” strategy, its applicability in PCV management is unsubstantiated.[28] Prospective studies to evaluate the long-term impact of tolerating a small amount of fluid in PCV are warranted. Till that time, in the presence of recurrent/recalcitrant disease activity on OCT, the patient can safely be advised anti-VEGF monotherapy. With the difficulties in gaining access to PDT at a global level and the associated complications associated with its repeated use[6–13] initiating and continuing the patient on anti-VEGF monotherapy is the best approach. Monotherapy with aflibercept is non-inferior to intravitreal aflibercept with rescue PDT, having comparable visual gains and polypyl closures at 24 months in the PLANET study.[3] Multiple studies have also demonstrated superior outcomes with the treat and extend aflibercept regimens in PCV.[19–23] Tamachi et al.[24] have shown significant improvement in vision with a reduction in central retinal thickness (CRT)
at 12 months with a treat and extend aflibercept in PCV. 60.8% of the study eyes achieved an administrative interval of 13 weeks, while an interval of 11 weeks, 9 weeks, 7 weeks, and 5 weeks was achieved by 7.8%, 3.9%, 11.8%, and 15.7% of eyes respectively. Thus, anti-VEGF monotherapy with three monthly doses followed by the treat and extend regimen,
especially with a more durable agent like aflibercept is the best long-term management approach to PCV. If the patient has been initiated on ranibizumab therapy with suboptimal response, switching to aflibercept therapy can be considered. The exact definition for non-responders is not consistent in literature. In the APOSIS guidelines, it has been defined as “eyes that received an induction or loading phase of 3-month anti-VEGF monotherapy from baseline and had persistent subretinal fluid (SRF) or intraretinal fluid (IRF) at their month 3 (± 1 month) assessments.” Saito M et al. showed evaluated 43 eyes with PCV refractory to three consecutive monthly ranibizumab injections after 12 months of initiating therapy. They noted significant visual improvement and a reduction in the CRT with a 50% regression rate of the polyps at three months. In another study, Saito M et al. also demonstrated a similar visual improvement, reduction in CRT and the CT, with regression of PL in 56.5% of 66 eyes which were switched to aflibercept from ranibizumab. Switching PCV eyes that were refractory or had recurrence following treatment with ranibizumab/bevacizumab with/without PDT to aflibercept resulted in disease activity remission in 70% of the eyes in an Indian study.

Treatment of extrafoveal, peripapillary, and peripheral polypoidal choroidal vasculopathy

What is the role of thermal laser in the management of PCV? What should be the laser parameters in treating PCV?

Summary of the guidelines (Recommendation 18)

Guidelines for the management of extrafoveal PCV:
1. Between 200 μ and ≤500 μ from fovea = PDT + 3 loading doses of anti-VEGF agents
2. 500 μ to ≤1000 μ from fovea =
   1. Lesion size >1000 μ: PDT + 3 loading doses of anti-VEGF agents
   2. Lesion size ≤1000 μ: Thermal laser (TL) + Anti-VEGF
3. Beyond 1000 μ from fovea = TL + Anti-VEGF.

Updated 2021 Recommendation 18

For lesions located between 200 μ and ≤500 μ from fovea and lesions >1000 μ which are located between 500 μ and ≤1000 μ from the fovea, the panel advocates to treat the patient with anti-VEGF monotherapy. No major changes from the 2018 recommendations are suggested for treating the other lesions. If the extrafoveal PCV is associated with significant serosanguineous elevation, the panel recommends to initiate the patient on anti-VEGF monotherapy, followed by TL once the fluid reduces.

Basis for the updated recommendations

For lesions beyond 1000 μ and smaller lesions (≤1000 μ) within 500 μ to ≤1000 μ from the fovea, a combination of TL with anti-VEGF therapy is still recommended. For the other forms of extrafoveal PCV, the updated literature supports the use of anti-VEGF monotherapy with aflibercept as previously described in the paper under recommendations 12–17. This is because of non-inferior results attained with aflibercept as compared to PDT with an absence of any PDT-related side-effects.

Summary of the guidelines (Recommendation 19)

Guidelines for the management of peripapillary and peripheral PCV:
1. Active symptomatic PCV: TL + Anti-VEGF agent
2. Active asymptomatic PCV: Consider treatment
3. Quiescent PCV: Observe.

Updated 2021 Recommendation 19

There are no proposed changes to the 2018 recommendations.

Summary of the guidelines (Recommendation 20)

Photocoagulation to the feeder vessel should be certainly considered in cases where it is visible on ICG and it is >500 μ from the center of the fovea. Treatment of the whole lesion is controversial and is based on the discretion.

Updated 2021 Recommendation 20

There are no proposed changes to the 2018 recommendations.

What is the role of OCT angiography in the management of PCV?

Updated 2021 Recommendation 21

OCT angiography (OCTA) can be utilized to provide complementary information to an ICGA regarding the morphology of the PL and BNN. It is an excellent tool to detect the BNN and monitor its response to therapy with serial scans. However, since the management of PCV is fundamentally driven by OCT biomarkers, the utility of an OCTA in a real-world setting is very limited. Moreover, the other factors constraining its widespread application in the management of PCV include lower PL detection rates, expensive imaging modality, and difficulties in image acquisition and interpretation due to hemorrhage, exudation, large PEDs, fibrosis, artifacts, and auto-segmentation errors.

Basis for the updated recommendations

OCTA is a non-invasive imaging modality for a detailed in vivo evaluation of the retinal and choroidal vascular structures. Wang M. et al. analyzed and compared the morphological characteristics of BNN and PL in PCV eyes on an OCTA and ICGA. They noted that OCTA was superior to an ICGA for the detection of BNN. However, the PLs were detected better on an ICGA. In literature, the rate of polyp detection on an OCTA ranges from 50%–92.5%. The lower detection rate of PL on an OCTA can be due to its variable flow, partially obstructed lumen, and segmentation errors due to irregular PEDs. Thus, although OCTA is advantageous for analyzing the morphology of the PCV complex, its utility in the real world is limited as it is not a highly sensitive imaging tool. Also, the information provided from an OCTA does not alter the decision-making process in PCV management, which is primarily OCT-driven.

Conclusion

Table 1 summarizes the key recommendations from the updated Indian PCV guidelines, which are based on evidence from the literature and the cumulative experience of the Indian retinal experts. These updated consensus guidelines for the management of PCV emphasize that this is a multifaceted disorder that needs an individualized therapeutic strategy. Timely imaging and interpretation of the same are vital to recognizing the extent and severity of the disease. Based on these factors, a tailored treatment should be planned for optimal outcomes in PCV management.
**Table 1: Summary of key recommendations for the management of polypoidal choroidal vasculopathy**

| Nomenclature | The terminology of “polyp” and “branching vascular network (BNN)” has been updated to “polypoidal lesion (PL)” and “branching neovascular network (BNV)” respectively. |
|-------------|----------------------------------------------------------------------------------------------------------------------------------|
| Imaging | ICGA is mandatory for clinical trials on PCV, but may not be essential in real-world management, especially considering the primary treatment with anti-VEGF injections in macular PCV. In real-world, ICGA is recommended only in case of poor response to anti-VEGF, or in hemorrhagic PCV where extrafoveal polyps can be laserered. In the absence of ICGA, a combination of near infrared (NIR) reflectance image and OCT can be utilized to determine the lesion involvement. In the absence of ICGA, a combination of three OCT features: sub-RPE ring-like lesion, en face OCT complex RPE elevation, and sharp-peaked pigment PED can be utilized with considerable accuracy for the diagnosis of PCV. Additional features such as a hyperreflective shallow irregular PED (double-layer sign), tomographic notched PED (complex or multilobular PED) with primarily subretinal fluid (SRF) with/without intraretinal fluid (IRF), and presence of thick chorioid based on the age and refractive error/axial length, a subfoveal choroidal thickness (SFCT) of ≥300 µm, and/or presence of focal dilated Haller’s layer vessels with overlying choriocapillaris attenuation are also indicative of PCV on SD-OCT. Performing an FFA is not mandatory in the management of PCV. OCTA can be utilized to provide complementary information to an ICGA regarding the morphology of the PL and BNN and for monitoring the response to therapy with serial scans. |
| Treatment | Due to the non-availability of PDT, anti-VEGF monotherapy is the definite choice for the management of active subfoveal and juxtapfoveal PCV. Based on level 1 evidence, aflibercept should be the preferred anti-VEGF agent for PCV. Brolucizumab therapy can be tried for PCV eyes refractory to both aflibercept and ranibizumab, given the limited evidence and higher rates of intraocular inflammation. Serial OCT is an important tool in following up the patients. Since PDT is not available, consider switching to aflibercept if the patient has already received three-loading doses of bevacizumab or ranibizumab with poor response. Use of the T&E regimen with longer-acting agents such as aflibercept is recommended to reduce the treatment burden and follow-up visits of the patient. |
| Thermal laser with anti-VEGF monotherapy can be considered in cases with extrafoveal polyps located beyond 1000 µ and smaller lesions (≤1000 µ) within 500 µ to ≤1000 µ from fovea, and to the feeder vessel in cases where it is visible on ICG and it is >500 µ from the center of the fovea. |

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Conflicts of interest
There are no conflicts of interest.

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