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REVIEW ARTICLE

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Clinical applications for intraoperative optical coherence tomography: a systematic review

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In this systematic review, we provide an overview of the current state of intraoperative optical coherence tomography (iOCT). As iOCT technology is increasingly utilized, its current clinical applications and potential uses warrant attention. Here, we categorize the findings of various studies by their respective fields, including the use of iOCT in vitreoretinal surgery, corneal surgery, glaucoma surgery, cataract surgery, and pediatric ophthalmology. The trend observed in recent decades towards performing minimally invasive ophthalmic surgery has caused practitioners to recognize the limitations of using a conventional surgical microscope for intraoperative visualization. Thus, the superior visualization provided by iOCT can improve the safety of these surgical techniques and promote the development of new minimally invasive ophthalmic surgeries. Landmark prospective studies found that iOCT can significantly affect surgical decision making and can cause a subsequent change in surgical strategy, and the use of iOCT has potential to improve surgical outcome. Despite these advantages, however, iOCT is still a relatively new technique, and beginning users of iOCT can encounter limitations that can preclude their reaching the full potential of iOCT and in this respect several improvements are needed.

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INTRODUCTION

A brief history of intraoperative optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive in vivo imaging technique used to obtain micron-resolution 2D and 3D images of ocular tissues. The first OCT images were published back in 1993 [1], and in the following three decades OCT went from an object of research to an indispensable tool for studying, diagnosing, and treating ocular diseases [2]. Relatively recent the OCT was first introduced in the surgical theater for intraoperative imaging and it has promising potential for a new paradigm shift in ophthalmic surgery.

OCT is a non-contact tomographic imaging modality that uses infrared light interferometry. The single interferograms (i.e., A-scan) are laterally combined to create a cross-sectional plane called a B-scan (Fig. 1) [3]. The high spatial resolution of modern OCT devices enables the clinician to easily differentiate tissues and layers and thank to the clear optical structures in the eye the signal is not perturbed. Furthermore, the use of OCT in practice is safe for both the patient and the clinician, as OCT does not emit harmful radiation. The development of OCT technology made systems increasingly compact and mobile, expanding its application from table-top devices, to slit-lamp mounted, handheld devices and integration into microscopes or probes [4–7].

The first experiences with intraoperative OCT (iOCT), acquired with a handheld OCT device, were reported in 2005 [5]. The first iOCT systems were either a handheld OCT device mounted to the surgical microscope or table-top devices were integrated into a microscope through its eyepiece [7, 8]. Similar integrated custom-designed OCT systems were also developed at Duke University and by Ehlers and colleagues at Cleveland Clinic [9–12]. This led to the development and commercialization of fully integrated systems into surgical microscopes with direct assessment capabilities, for example the inclusion of a heads-up display in the eyepieces [10, 12–14].

The technical possibilities of iOCT evidently underwent significant improvement. More recently, also the clinical possibilities for using OCT during surgical procedures are taking shape, and there is a growing body of research in all ophthalmic surgical domains that can be used to evaluate the utility and added value of iOCT in ophthalmic surgery. Here, we provide a comprehensive systematic review of the current knowledge regarding iOCT and its applications.

METHODS

A structured literature search of titles and/or abstracts in Pubmed and Embase was performed on September 29th 2020. The literature search was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15]. The search terms included: "optical coherence tomography ocular surgery", "intraoperative optical coherence tomography", "microscope-integrated optical coherence tomography" "intraoperative optical coherence tomography eye", and all relevant synonyms and abbreviations. No date restrictions were set. The titles and abstracts of all retrieved

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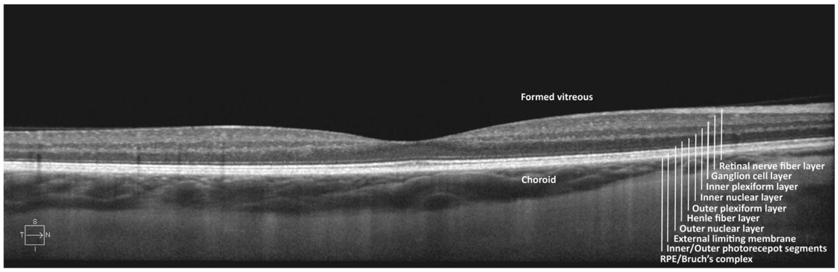

Fig. 1 An OCT cross-sectional image (B-scan) of a healthy human retina. The different retinal layers can be distinguished using the reflective properties of the layers and tissues. These reflective properties result in hyperfluorescent and hypofluorescent tissues, and the image is typically converted to a grayscale (shown) or pseudocolor image (not shown) in order to highlight the retinal layers.

articles were screened using pre-specified criteria for inclusion by two reviewers (M.M. and N.W.). The references of identified articles were manually checked to find potential relevant studies. Studies were included for full-text review and qualitative analysis if they reported on clinical applications and outcomes of iOCT. Studies were excluded if they reported non-original research, reported on cadaver/non-human/mock eyes, or were either a non-peer-reviewed article, review, comment, case report, case series with less than 5 eyes, and/or were not published in English.

The included studies were independently evaluated by the same two reviewers (M.M. and N.W.) to assess; the strength of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEM) 2011 guidelines, the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines, and were critically appraised using the Joanna Briggs institute critical appraisal tool for case series, as the majority of identified studies were classified as case series [16–19]. Disagreement between the reviewers was resolved by discussion and a third reviewer (R.W.) was consulted if necessary. The included studies were qualitatively analyzed and grouped in the following domains; clinical decision making, vitreoretinal surgery, corneal and refractive surgery, cataract surgery, glaucoma surgery, pediatric ophthalmic surgery. The study design, number of subjects, level of evidence, critical appraisal, intervention and main findings related to iOCT were summarized in a table for each of the domains (see Supplementary Data). The studies reporting on retinal membrane peeling and macular hole surgery, and refractive surgery were summarized in separate table.

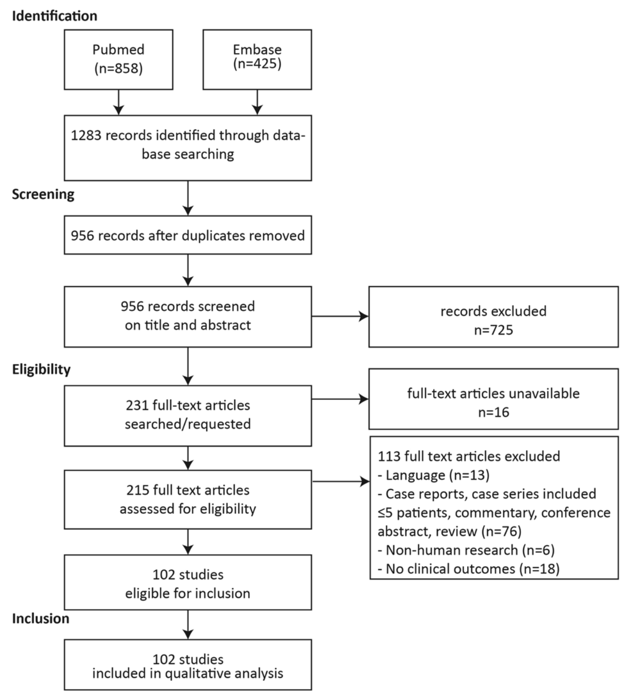

Fig. 2 The PRISMA flowchart of the literature search. Flow diagram of study identification, study exclusion, full-text review, and study inclusion.

RESULTS

A total of 1283 studies were identified after the initial literature search. A detailed overview of the selection process and reasons for exclusion after full-text screening is shown in Fig. 2. After title and abstract screening 231 full-text articles were assessed for eligibility. For 16 articles the full-text was not available and attempts were made to retrieve these articles using other databases without success. Finally, after full-text review 102 articles were included for qualitative analysis. A detailed overview of the included studies, design, level of evidence, critical appraisal, and main findings can be found in the Supplementary Data. In the following subsections the outcomes of included studies are presented within their respective domain.

FEASIBILITY OF INTRAOPERATIVE OCT AND IMPACT ON CLINICAL DECISION MAKING

The technological advancements of OCT made the systems increasingly mobile and compact, however, implementation of iOCT faced operational hurdles which prevented widespread adoption. First, the conditions for image acquisition are challenging, such as a sterile environment and supine patient. Second, image acquisition delays surgical workflow. Third, the OCT device is a significant investment with limited understanding of the benefits [20]. In this section we assess and the impact of iOCT on clinical decision making and review the different iOCT devices in use.

Impact of intraoperative OCT on clinical decision making

The introduction of iOCT in the surgical theater has offered surgeons a previously unreachable source of information (Fig. 3). A majority of early research focused on how this information was used by surgeons to aid clinical decision making (see Supplementary Table 1). The landmark prospective intraoperative and perioperative ophthalmic imaging with optical coherence tomography (PIONEER) and Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/ Integrated OCT Visualization During En Face Retinal and Ophthalmic Surgery (DISCOVER) studies by Ehlers et al. thoroughly investigated the impact of iOCT on clinical decision making [20, 21]. In the PIONEER study the iOCT image altered surgical decision making in 68% of posterior lamellar keratoplasty and 46% of retinal membrane peeling procedures [20]. Similarly, in the DISCOVER study the OCT

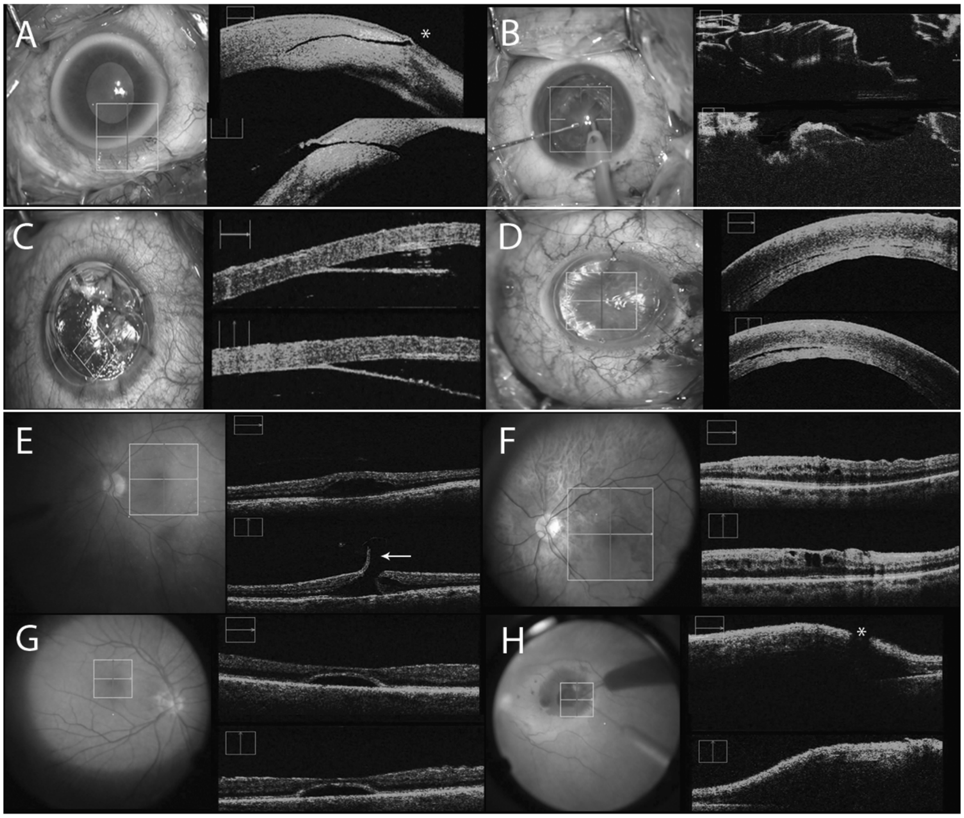

Fig. 3 Examples of iOCT use. In each panel, the picture on the left shows an en face microscope image, and the corresponding live OCT images are shown on the right in two perpendicular planes (indicated by purple and turquoise crosshairs). An example of a self-sealing incision (indicated by the asterisk in **A**) and assessment of the groove depth during phacoemulsification (**B**). Separation of the stroma and Descemet's layer during deep anterior lamellar keratoplasty (**C**), and assessment of the interface fluid in Descemet stripping automated endothelial keratoplasty (**D**). The thin layer of hyporeflectivity between the graft and stroma indicates the presence of fluid. Intraoperative macular hole formation (**E**) with a membrane strand still attached to the retina (indicated by the arrow) and intraretinal cystic changes (**F**). The green indocyanine staining shows an incomplete staining of the inner limiting membrane, indicating the presence of an epiretinal membrane. Which can be confirmed in the OCT image. Retained subretinal fluid (**G**) and tPA injected for submacular hemorrhage (**H**); the asterisk in **H** indicates the needle injection site, and the absolute shadowing in the microscope image in **H** indicates the presence of high-density material.

image provided valuable feedback in ~60% of surgeries, thereby altering surgical decision making in 46% of anterior segment surgeries and 29% of posterior segment surgeries [21]. The benefit of OCT-probes has not been demonstrated in large cohorts, but Mura et al. reported that using a OCT probe it was possible to image the retinal periphery, vitreous base and ciliary body, which would be challenging or even impossible using a conventional surgical microscope or other iOCT systems [4].

Other studies reporting on the impact of iOCT on clinical decision making report similar results as the PIONEER and DISCOVER study [8, 14, 22–25]. The results of these studies suggest that the iOCT fills the gaps in surgical information and these insights may improve quality of care and surgical efficiency. Examples of surgical information provided by the iOCT included assessment of the completeness of retinal membrane peeling and adherence of posterior lamellar keratoplasty grafts. A detailed review of the impact and benefit of iOCT is provided in the following subsection for each surgical domain. Notwithstanding, the bias in the design of these studies deserves attention. In all studies the iOCT system was available to use at the surgeons discretion and in none of the studies the researchers randomized for iOCT use. The evidence of the benefits of iOCT therefor remain indirect. In addition, the availability of iOCT may also lead to potential problems, such as data overload and fixation on irregularities of which the clinical relevance is unclear.

Intraoperative OCT devices

Three types of iOCT devices are currently used in practice (i.e., (mounted) handheld, microscope-integrated, and instrument/probe integrated) and these device types have their respective benefits and limitations. Handheld devices can be used in concordance to a surgical microscope, but also as a stand-alone device [20]. This flexibility is also their most notable advantage compared to dedicated iOCT platforms. However, the handling of a handheld device can be challenging because the system, if not mounted, is unstable which makes image acquisition difficult and has a steep learning curve [5, 20, 26]. To this end handheld devices are mounted (i.e., attached to the surgical microscope) and can be moved in place for image acquisition. The mounted systems use the stability and precise maneuverability in the x, y, and z plane offered by the surgical microscope, thereby significantly improving the speed, accuracy and reproducibility of iOCT imaging [20]. In the PIONEER study Ehlers et al. successfully obtained intraoperative images using a mounted handheld device in 98% of the eyes with a minimal impact on surgical workflow [20]. The median time to set up the iOCT was 1.7 min and the median time the surgery was paused measured 4.9 min per scan session [20].

Notwithstanding, pausing the surgery for image acquisition remains a major disadvantage of handheld systems. Moreover, during the PIONEER study a technician was present to support imaging and image acquisition may be more complicated without support [20].

A microscope-integrated iOCT has several advantages compared to handheld devices. First, the integrated system can be used can be used without pausing the surgery and during surgical maneuvers, thereby disrupting the surgical workflow less and lowering the threshold for its use. Second, integrating into the surgical microscope facilitates independent use by the surgeon without support of a technician. Third, the design creates more possibilities to integrate tools and algorithms to enhance surgery, such as decision aids and surgical guidance tools [12].

Lastly, OCT technology has advanced to the point it can be integrated into probes and instrument for intraocular use. In contrast to handheld and integrated systems OCT probes and OCT-integrated instruments were developed to provide maximal flexibility during vitreoretinal surgery [4]. Using an OCT probe or instrument, the ciliary body and peripheral retina can be imaged easily, and image acquisition is not affected by the presence of cloudy media [4]. Despite these advantages, however, these probes and instruments have several disadvantages as well, including a limited field of view, a vulnerable design, costly non-reusable probe tips, relatively high risk of contamination, difficult image acquisition, and a steep learning curve for the surgeon [4, 27, 28].

VITREORETINAL SURGERY

The use of OCT revolutionized the diagnosis and treatment of vitreoretinal diseases, and has become an indispensable tool in this field [2]. As result, iOCT was initially targeted primarily to vitreoretinal surgeons. Despite early research interest, iOCT has not yet enjoyed the same popularity as their table-top counterparts. Nevertheless, the body of research regarding iOCT during vitreoretinal surgery is extensive. Several studies have shown that the findings on the iOCT image can aid and alter surgical decision making in about 30–40% of vitreoretinal surgeries [20, 21]. The iOCT images provide valuable insights in tissue dynamics and alterations following surgical interventions. As a diagnostic device the iOCT can be used to evaluate the retina for underlying conditions [29]. For example, in cases with a vitreous hemorrhage, pathology can be excluded or—if possible—treated [30, 31]. Moreover, the direct imagery of iOCT allows for early detection of adverse events and management of these events [32–34].

The use of iOCT has been reported for a variety of routine vitreoretinal procedures such as macular surgery and retinal detachment surgery (see “Retinal membrane peeling and macular hole surgery” and “retinal detachment surgery”), but also for challenging surgeries which entail a considerable risk of misplacement, incorrect removal of tissue, scar tissue formation, and/or poor surgical outcomes. Examples of challenging interventions were the in-depth visualization and assistance of iOCT is reported are; the placement of retinal implants and medical devices in the vitreous cavity [35, 36], retinal biopsies [37], cystotomy for deroofing macular cysts [38], and subretinal and submacular injections [39]. In particular, the use of subretinal and submacular injections is expected to increase and are crucial for novel gene therapies. The iOCT image allows for the genetic material to be delivered with improved accuracy [39]. The complete overview of included studies and outcomes can be found in Supplementary Table 2 (macular surgery) and 3 (vitreoretinal surgery).

Retinal membrane peeling and macular hole surgery

The peeling of membranes of the retina (e.g., internal limiting membrane (ILM), epiretinal membrane (ERM), and pucker peelings) is a frequent performed procedures and among procedures in which the iOCT is most utilized [20, 21]. The iOCT can be used to determine the starting point for the peel, to check for retina/macular hole formation after peeling, and/or to confirm that the peel is completed (see Supplementary Table 2) [20, 21, 33, 40–44]. Several studies revealed a considerable disagreement between the surgeon’s observation and the OCT image in regard to peel completeness [20, 21, 41, 43, 44]. For example, in the DISCOVER study the iOCT showed residual membranes when the surgeon believed that the membrane was fully peeled in 20% of the cases. Conversely, in 40% of cases in which the surgeon suspected a residual membrane, iOCT revealed that the peel was complete, preventing the need for unnecessary surgical action [21]. Membrane peeling without the use of chromovitrectomy dyes has also been performed, albeit with limited success [41, 43]. Leisser et al. reported successful peeling of the ERM without the use of dyes [43]. Although no significant differences in outcomes were found between the use of dyes and dye-free peeling. Moreover, chromovitrectomy dyes were still necessary for staining the ILM and posterior hyaloid. Another factor that may limit the success of performing dye-free iOCT-assisted membrane peeling is the shadow that metallic instruments cast over the peeling area, as well as suboptimal visualization of thin membranes [21, 41]. The use of intravitreal dyes to enhance OCT contrast (i.e., dyeing the membranes to improving visualization on the iOCT image) has shown potential for iOCT-assisted membrane peeling and may improve surgeon feedback on the completeness of the peel. Indocyanine green, which is a widely used dye, enhances the reflectivity of the ILM and ERM (contrast ratio increased from 0.907 to 1.42, $p < 0.001$) [45]. Similarly, tissue reflectivity improved using triamcinolone and prednisolone acetate, though all contrast agents resulted in shadowing of the underlying tissue [45].

Furthermore, iOCT has also been used to increase our understanding of tissue-instrument interactions and gain insight in retinal alterations after membrane peeling. The retina is a delicate tissue that can be damaged easily by surgical instruments. This has led to the introduction and preferences for using minimally traumatic instruments in recent years. On the other hand, no association has been found between increased retinal damage and subsequent alterations when using a specific type of instrument (e.g., pick, loop or duster) during membrane peeling [11, 46–48]. During and immediately after peeling the ILM or ERM significant iatrogenic retinal alterations could be detected on the iOCT scans (see Supplementary Table 2), though the detected alterations resolved rapidly after releasing traction or after surgery [44, 46, 47, 49–56]. The impact of these transient alterations is not yet fully understood, but studies have found no association with long-term worsening of functional or anatomical outcomes [47, 49, 52–54, 57].

The utility of iOCT during surgical treatment of macular holes has also received extensive attention and the shows promising results (see Supplementary Table 2). During macular hole repair surgery the release of traction, efficacy of the tamponade, and closure of the hole can be directly assessed on the iOCT image [25, 40, 58]. In addition during inverted flap procedures the positioning of the flap in the macular hole can be observed, even after fluid-air exchange [25, 33, 59]. Assessing efficacy of tamponade and hole closure may be useful to tailor face-down positioning after surgery [60]. Furthermore, using the iOCT Kumar and Yadav were able to identify a novel intraoperative sign predictive of macular hole closure. Kumar and Yadav named this sign the ‘hole-door-sign’: residual vertical tissue pillars at the macular hole edge after ILM peeling [61]. Eyes with the hole-door-sign had a 100% rate of closure without an neurosensory defect compared to 60% of the eyes without the hole-door-sign [61]. The studies of Inoue et al. and Tao et al. confirmed the predictive value of the hole-door-sign for macula hole closure, however, the authors reported contradicting results regarding the post-operative visual acuity in eyes with the hole-door-sign [62, 63].

The use of iOCT also provided valuable insights in macular hole dynamics. After ILM peeling the macular hole height and central hole diameter were reported to remain stable, whereas hole volume, base diameter, base area, top/apex diameter, and top/apex area increased compared to before ILM peeling [46, 51, 64]. Based on these insights in macular hole dynamics Ehlers et al. investigated the predictive value of retinal tissue dynamics for early macular hole closure. Their predictive model had an area under the curve of 0.974 and the most robust predictors for early macular hole closure were intraoperative change in macular hole volume, intraoperative change in minimal width, and pre-incision minimal width [65]. Both the hole-door-sign as well as the predictive model of Ehlers et al. may be a first step towards customized surgery [61, 65]. In this regard, the use of volumetric iOCT may facilitate implementation for these and similar tools analyzing tissue dynamics [66, 67].

Retinal detachment surgery. During surgical repair of retinal detachment (RD), the iOCT images can provide valuable information and aid clinical decision making, particularly in complex cases, as was shown by Abraham et al. [23]. They reported that in 50% of complex RD cases the iOCT provided valuable feedback – which altered surgical management in 12% of cases – compared to 21% in non-complex cases ($p = 0.01$) [23]. In cases of RD with macular involvement, significant amounts of occult non-resolving sub-macular fluid have been observed after perfluoro-n-octane instillation, direct drainage, or a drainage retinotomy [68]. The presence sub-macular fluid could delay visual recovery, but does not appear to impact postoperative functional or anatomical outcomes, specifically the ellipsoid integrity [69, 70]. The significant changes of the retinal tissue have been found resembling alterations observed after macular surgery, ranging from hyper-reflectance to disruption of the retinal layers [71]. However, the majority of detected alterations did not impact the clinical decision making in both RD and macular surgery, because it is not possible or unclear how to prevent or resolve these alterations.

CORNEAL AND REFRACTIVE SURGERY

The use of iOCT in corneal surgery is rapidly growing in popularity. Specifically, easy imaging of the cornea contributes to the low threshold for adopting the use of iOCT in corneal surgery. The corneal surgeon experiences only minimal loss of focus when using iOCT, and the optical properties of the cornea minimize shadowing of the image. The principal application of iOCT is in selective keratoplasty, which is considered to be technically demanding, particularly in cases with a cloudy or edematous cornea. The PIONEER and DISCOVER study showed the advantages associated with access to iOCT technology during selective keratoplasty; specifically, the new information provided by iOCT led a critical change in surgical decision making in, respectively, 48% and 43% of lamellar corneal surgeries [20, 21]. In this section the applications and benefits of iOCT in corneal and refractive surgery are reviewed. The detailed overview of the included studies and outcomes can be found in Supplementary Tables 4 and 5.

Anterior corneal surgery

Deep lamellar anterior keratoplasty (DALK) is the selective transplantation of the corneal stroma, leaving the recipients Descemet membrane and endothelium in place. During DALK, the Descemet's membrane and anterior stroma must be completely separated by either manual or big bubble dissection. However, both methods for separating the layers are at risk of complications and separation of the layers is difficult to visualize using the en-face microscope view. In particular, successful big bubble formation in particular is dependent on the depth of the dissection plane for cannula placement [72]. The iOCT enables the surgeon to directly assess the depth of the dissection plane and if necessary place additional cuts or reposition the cannula [73]. Additionally, after injecting air between the corneal layers the surgeon can confirm separation of the layers and Descemet's membrane integrity [74, 75]. Initials reports using iOCT during DALK showed that a deeper trephination depth can be achieved and the cannula can be placed closer to the Descemet's membrane (successful big bubble: 90.4 ± 27.7 µm, failed big bubble: 136.7 ± 24.2 µm, $p < 0.01$), leading to a high rate of successful big-bubbles (≥70%) [72, 74]. Moreover, the use of iOCT enables the surgeon to attempt manual dissection in the case of an emphysematous opaque cornea after a failed attempt using the big bubble method [74, 75]. Lastly, Guindolet et al. reported that femtosecond laser DALK with iOCT assistance resulted in a 100% success rate with respect to big bubble formation, with no perforations, in eighteen DALK procedures [76]. They attributed this success to the accuracy of femtosecond laser cuts combined with direct assessment of corneal thickness using iOCT.

Similarly to assessing the dissection plane in DALK surgery Zakaria et al. used iOCT to guide dissection depth during pannus removal in limbal stem cell transplantation [77]. During surgery OCT pachymetry maps were made to assess how much tissue was removed and prevent accidental corneal perforation. In all 8 cases the pannus was completely removed and no corneal perforations were recorded [77].

Posterior lamellar corneal surgery

Notable advantages of iOCT in corneal surgery are observed during posterior lamellar keratoplasty, such as Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK), in which the posterior corneal layers are selectively replaced by a partial corneal graft [78]. A relative frequent and burdensome adverse event is postoperative detachment of the graft, which often necessitates additional surgical procedures. Although the underlying cause of graft detachment is considered multifactorial, though interface irregularities and/or the presence of fluid in the interface are believed to impede proper attachment of the graft [79]. In addition, interface fluid could lead to textural interface opacities and could negatively impact visual acuity [80]. The presence of interface fluid is not always evident in the en-face microscope view and the use of iOCT allows the surgeon to assess the interface in high detail, detect areas of non-adherence, or folds during surgery, which may require additional interventions (Fig. 4) [26, 81–84]. For example, in 46 of 84 DSAEK procedures of the DISCOVER study persistent interface fluid was visualized, in which the surgeon deemed the graft well-attachment [21]. In addition, the iOCT image provides insight in the efficacy of surgical maneuvers to reduce interface fluid and promote graft adherence, including: corneal swiping, venting incisions, and over-pressurizing the ocular globe [82, 85, 86]. All these maneuvers were reported to significantly reduce interface fluid in DSAEK. However, the independent use of prolonged overpressure of the globe may only marginally reduce interface fluid. Titiyal et al. reported that interface fluid persisted after 8 min of overpressure, whereas by combined overpressure and corneal swiping interface fluid disappeared within 3 min [87]. Recently, we performed a similar study in which the use of overpressure in DMEK surgery was evaluated compared to using a minimal pressurization time. Similarly, our results indicated that refraining from prolonged overpressure during DMEK increases surgical efficacy without increasing the risk of postoperative adverse events [79]. Refraining from prolonged overpressure does not appear to increase risk of graft detachment, reduces surgical time and may prevent damage to the optic nerve head, especially relevant for patient with pre-existing glaucoma.

Furthermore, iOCT can be useful while determining orientation, unfolding, and positioning the graft during DMEK [84, 88, 89]. Proper orientation of the graft must be determined in order to ensure functional graft adhesion (Fig. 5). Currently used signs/methods (e.g., the Moutsouris-sign, stamps or circular cuts) are not

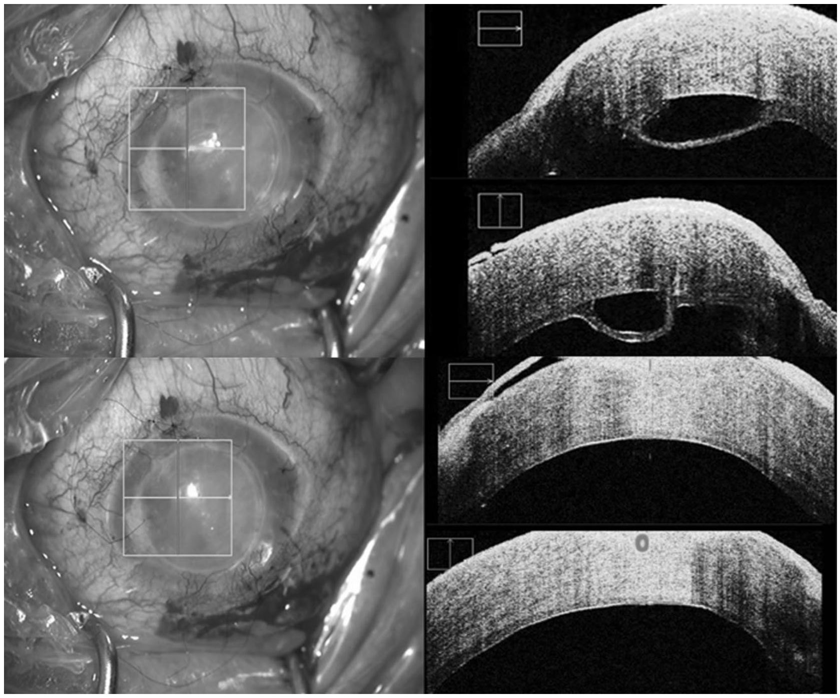

Fig. 4 iOCT reveals an interface fluid. In each panel, the picture on the left shows an en face microscope image, and the corresponding live OCT images are shown on the right in two perpendicular planes (indicated by purple and turquoise crosshairs). **A** An example of fluid/gas in the interface of a Descemet stripping automated endothelial keratoplasty (DSAEK). **B** The same cornea shown in A, with a completely attached DSAEK graft.

always self-evident and poor visualization hinder proper assessment [88, 89]. Not to mention, both stamps and cuts damage the graft resulting in endothelial cell loss [79]. More recently, iOCT has been used to determine graft orientation as the iOCT signal is not perturbed by cloudy media [79, 90, 91]. The natural rolling behavior of DMEK grafts can be well appreciated on the iOCT image, thereby preventing the need to manipulate, cut, or mark the graft to determine the orientation, subsequently preventing endothelial cell loss. In addition, both Saad et al. and Patel et al. reported that iOCT resulted in a shorter duration for unscrolling and positioning the DMEK graft, thereby reducing graft manipulation and improving surgical efficiency [88, 91].

Incorporating iOCT-guidance in posterior lamellar keratoplasty can optimize both the surgical techniques and surgical outcome. Nevertheless, care should be taken with iOCT-guided surgery, as it can lead to more (rigorous) manipulation and a more aggressive surgical approach, potentially leading to graft damage [86]. For example, the high-resolution images provided by iOCT can reveal small folds, non-adherence, and interface irregularities for which the clinical significance is yet unclear.

Corneal crosslinking and refractive surgery

Corneal crosslinking (CXL) is now the first-line treatment for progressive corneal ectasia, particularly keratoconus [92]. During CXL the penetration of riboflavin in the corneal stroma a key factor that determines treatment efficacy and iOCT has been successfully used to visualize the penetration depth of riboflavin by the noticeable hyper-reflectance of riboflavin [93]. Importantly, the depth of riboflavin penetration was lower in epithelium-on CXL (149.39 ± 15.63 µm) compared to epithelium-off procedures (191.04 ± 32.18 µm), suggesting that penetration depth could be used to determine treatment efficacy [93].

Several studies reported successful use of OCT to measure corneal thickness and/or corneal dissection depth during CXL and refractive surgery [94, 95]. Compared to the current gold standard for measuring corneal thickness, ultrasound pachymetry, OCT pachymetry has several advantages. OCT pachymetry is a non-contact technique that uses the corneal apex reflection for alignment and a larger area of the cornea can be measured. This is relevant for CXL as it allows the thinnest part of the cornea—which is often paracentrally located—to be detected more easily and obtaining a thickness map of the entire cornea reduces the risk of inadvertently damaging the corneal endothelium due to UV radiation in CXL [94, 96]. The agreement of measurements between OCT pachymetry and ultrasound pachymetry is high (intraclass correlation coefficient 0.80), and OCT measurements are highly repeatable. Therefore, iOCT pachymetry provides a more standardized measurement, with higher accuracy and negligible risks compared to ultrasound pachymetry [97]. Furthermore, Siebelmann et al. demonstrated the use of iOCT for determining the depth during corneal laser dissection and may be particularly beneficial for therapeutical corneal ablation, because preoperative OCT scans can become inaccurate during the docking process [98].

Titiyal et al. and Torbey et al. described the use of iOCT to assess the position and vaulting of implantable collamer lens [99, 100]. In both studies a high significant correlation was found between intraoperative and postoperative vaulting (Titiyal et al. $r = 0.954$; $p < 0.001$; Torbey et al. $r = 0.81$, $p < 0.001$) [99, 100]. This is clinically relevant, given that extreme vaulting is associated with a postoperative residual refractive error or postoperative complications such as cataract or iatrogenic acute glaucoma, which may necessitate removal of the lens [99].

CATARACT SURGERY

Although the use of iOCT during cataract surgery is still its infancy, it has high potential. Worldwide, cataract surgery is the most commonly performed form of ophthalmic surgery and is arguably one of the safest [101]. In this section we review the current applications and potential of iOCT during cataract surgery. A detailed overview of included studies and outcomes can be found

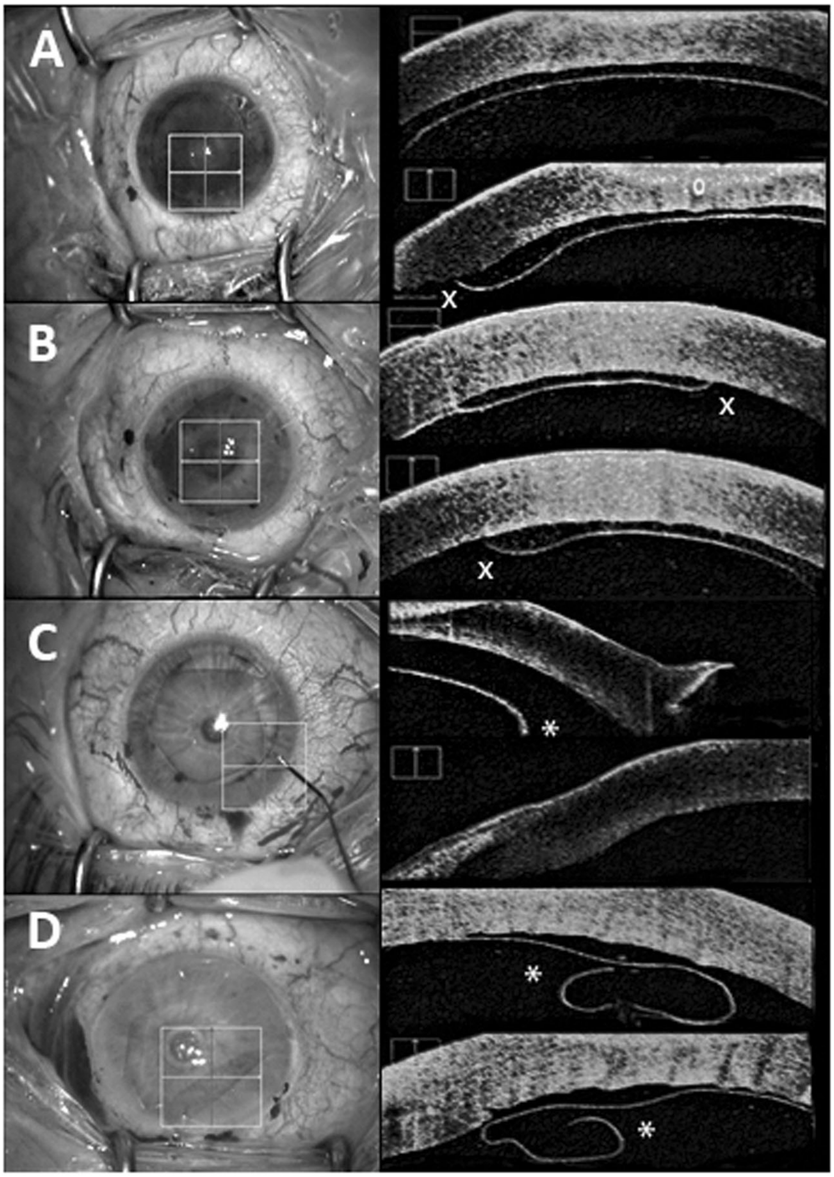

Fig. 5 Use of iOCT to observe intraocular graft geometry in two perpendicular planes (purple and turquoise crosshairs) in high detail. Shown are four examples of an en face microscope view (left column) and the unaltered OCT image (right column). The naturally curling motion of the graft in Descemet membrane endothelial keratoplasty can be used to determine the graft's orientation. In panels **A** and **B**, the "x" indicates were the graft curls towards the recipient's cornea, indicating proper orientation of the graft. In panels **C** and **D**, the asterisks indicate were the graft curls away from the recipient's cornea, indicating incorrect (i.e., upside-down) graft orientation.

in Supplementary Table 6. The learning curve associated with performing microsurgery—including cataract surgery—is considered both steep and demanding [102]. In this respect, the use of iOCT could improve this procedure and serve as an aid during cataract surgery training. Compared to conventional surgery, iOCT provides superior tissue visualization of the groove depth and construction of self-sealing corneal incisions, thereby enabling the supervisors to directly guide the trainee and provide feedback in real time [103, 104]. Notwithstanding, no study to date has been performed investigating the use of iOCT during cataract surgery training.

The use of iOCT may also benefit experienced cataract surgeons for timely detection and management of surgical complications. For example, Titiyal et al. reported that Descemet membrane detachment after stromal hydration could only be observed using iOCT [104]. This is particularly relevant in the case of extensive Descemet membrane detachment, which is usually not self-resolving. Likewise, Cendelin et al. reported that stromal hydration negatively impacted incision architecture in 14 of 69 eyes and resulted in wound gaping in two cases, which subsequently required intervention [105]. Additionally, the OCT image could aid surgeons in confirming placement of the intra-ocular lens (IOL) in the capsule bag [103, 106], detecting capsular defects [107], identifying true posterior polar cataract, and confirming separation of the posterior polar plaque and capsule [103].

Importantly, studies have shown the potential of iOCT in optimizing the refractive outcome following cataract surgery. The iOCT images and the associated data provide information regarding the lens' intraocular position and can be used to optimize IOL calculations and future IOL designs. Hadded et al. reported a strong correlation between the meridian lens position and anterior chamber depth (ACD) [108]. Similarly, Hirschall et al. found that intraoperative ACD measured using OCT was more representative for postoperative ACD and the intraoperative ACD was a significantly better predictor for postoperative manifest refractive outcome [109–111]. Integrating iOCT data into current IOL power calculation formulas can improve refractive outcome [111]. Hirschall et al. showed that combining preoperative and intraoperative ACD measurements refractive surprises can be reduced with 2.8 percent-point and would have resulted in a different IOL power in 7.1% of cases [111].

Furthermore, the iOCT has led to new insights regarding morphology of cataracts and effects of lens fragments. In 2016, Amir-Asgari et al. assessed the effect of swirling/pinballing lens fragments in the anterior chamber and the endothelial damage that these fragments can cause, finding that smaller particles with higher velocity tend to inflict more damage than larger, slower moving particles [112]. Titiyal et al. used the iOCT to investigate morphological characteristics and dynamics of white cataracts and posterior polar cataracts [113, 114]. Distinct characteristics of white cataract that were observed on OCT in different degrees included; the convexity of the anterior capsule, arrangement and reflectance of cortical fibers, presence of clefts, and homogenous ground glass appearance [114]. In posterior polar cataract they identified differences in delineating of the posterior capsule, reflectivity of the posterior polar opacity and underlying capsule, and adherence of the opacity to the posterior capsule [113]. Based on these features the authors propose new classification systems for these types of cataract, thereby aiding patient care and future research.

GLAUCOMA SURGERY

The goal of glaucoma surgery is to either increase the outflow of aqueous humor by drainage into the subconjunctival space or improve trabecular outflow [115]. Unfortunately, however, scleral tissue is poorly transparent to light in the visible and infrared spectrum; thus, initial experiences using iOCT in glaucoma surgery were rather unsuccessful in terms of providing the surgeon with improved visualization. Nevertheless, several studies have reported on the added value of iOCT in glaucoma surgery.

Most of the studies investigating the use of iOCT during glaucoma surgery consist of case reports or small case series, reporting on bleb needling [116], trabeculectomy [117], canaloplasty [118], long-tube glaucoma drainage devices [119], and angle surgery [117]. Only three studies describing iOCT use during ab-interno trabeculotomy met the inclusion criteria for this review (see Supplementary Table 7). In all three studies the authors reported that cleft and incision patterns could be observed on the OCT image after trabecular meshwork tissue removal, thereby providing an indication of the surgery's success [120–122]. Notwithstanding, all three studies noted that image acquisition was challenging and they needed a gonioprism lens for visualizing the anterior chamber angle. Only Junker et al. reported successful visualization of the trabecular meshwork without a gonioprism lens in 2 of 5 surgeries, although acquiring images took 15 min compared to 2–4 min for surgeries with a gonioprism lens [120]. Visualizing deeper angle structures or structures embedded in dense scleral tissue is both demanding and time-consuming—or simply not possible—using currently available OCT devices, as dense scleral tissue is impenetrable to the wavelength used in iOCT devices, thereby completely shadowing the OCT image [123]. Possible solutions to overcome the visualization challenges and improve utility of the iOCT include using a longer wavelength for better tissue penetration and adjustable scanning directions.

Furthermore, new forms of microscopic and minimally invasive surgical glaucoma procedures are coming on the market which could benefit from iOCT; small devices (e.g., stents an microshunts) often must be placed correctly in either the trabecular meshwork or the subconjunctival space/anterior chamber [124]. Placing these devices in the suprachoroidal space is another option, but is currently hampered by poor clinical success. It has not been investigated if iOCT could improve the results of suprachoroidal placements of glaucoma devices.

PEDIATRIC OPHTHALMIC SURGERY

In infants, young children, and mentally impaired patients, performing an OCT examination is often difficult—or even impossible—using a table-top OCT device. Thus, the introduction of mobile OCT devices, including handheld and microscope-integrated devices, made it possible to exam these patients [125]. This is particularly valuable for examining new-borns and infants with a congenital eye disease, in which early structural changes were previously difficult to examine and study. Using iOCT makes it possible to examine ocular structures and the extent of the underlying pathology (see Supplementary Table 8). Furthermore, if surgical intervention is indicated, iOCT can be used to determine the degree of intervention required and assist clinical decision making (Fig. 6). For example, Hong et al. used iOCT during surgical reconstruction of the anterior segment in infants with Peter's anomaly, finding that iOCT image led to a change in the surgical approach in 7 out of 33 cases (21%), as well as providing new information compared to both the preoperative examination and the en face ophthalmic microscope view [126]. Importantly, the use of iOCT prevented removal of the crystalline lens in 5 patients [126]. The authors concluded that disease severity in Peter's anomaly is often overestimated without the benefit of OCT examination, including overestimating the angle closure, ACD, and iridocorneal adhesion, leading the authors to conclude that OCT should be incorporated into the standard care of infants with Peter's anomaly [126]. Similarly, Bradfield et al. used iOCT to determine obstruction of the anterior chamber angle or Schlemm's canal during pediatric glaucoma surgery [127]. In 8

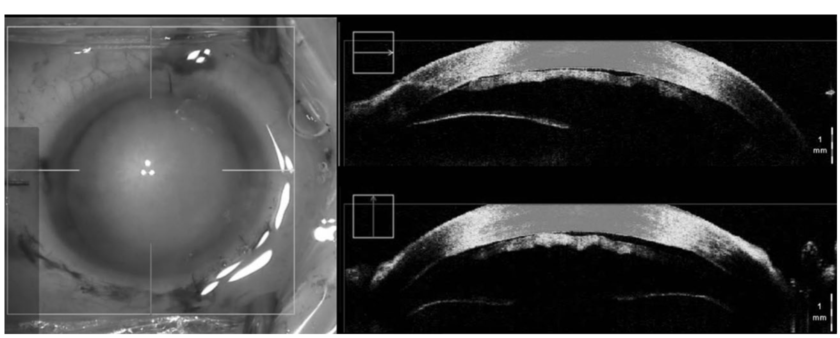

Fig. 6 A 3-month-old infant with severe posterior polymorphous dystrophy. Note that the opaque cornea precludes visualization of the anterior chamber. Shown at the right are two perpendicular planes of the corneal OCT image (the turquoise and purple crosshairs). In both OCT planes, the DSEK graft is visible as a tissue mass directly under the hyper-reflective cornea. The graft is stretched, but not yet completely attached, prior to the injection of gas. Note that iOCT was invaluable for performing endothelial keratoplasty in this infant.

of 13 glaucomatous eyes an obstruction could be observed on the OCT image and in cases with an absent Schlemm's canal the procedure could be directly altered or reverted to a tube-shunt procedure [127].

Furthermore, Sharma et al. compared a cohort of iOCT-assisted pediatric keratoplasty's to a historical cohort [128]. The use of iOCT affected surgical decision making in 45% and 33% of anterior and posterior lamellar keratoplasty [128]. During penetrating keratoplasty significant more concomitant procedures were performed in the iOCT-assisted cohort (29/40) compared to the historical cohort (4/15) [128]. Moreover, the incidence of secondary or repeated interventions was significantly lower in the iOCT-assisted group compared to the historical cohort ($p = 0.04$) [128]. Similar, Siebelmann et al. found that iOCT proved very useful for diagnosis in pediatric patients and in 5 cases the decision to treat was directly the result of the OCT image [129].

Lastly, Pihlblad et al. investigated the potential of iOCT during pediatric strabismus surgery [130]. The extraocular muscle insertion distance was measured with different OCT devices and compared to measurements using a calliper in 19 pediatric patients. In 71% and 89% of cases the muscle insertion point was accurately visualized with, respectively, a handheld and microscope-integrated OCT device [130].

Discussion and conclusion: future directions

In this review, we summarized the current knowledge and opportunities provided by OCT during surgery. New research shows that iOCT can actively support the surgeon by providing direct, real-time feedback during surgery. This enables the surgeon – with unprecedented in-depth resolution – to review events, interactions and tissue changes intraoperatively. OCT imaging can improve the safety of surgical procedures, promote the development of novel surgical procedures, and stimulate evidence-based medicine. The use of intrasurgical biomedical imaging has drastically changed other fields of surgery and is increasingly a cornerstone of new procedures [131, 132]. In our opinion iOCT has a similar potential to advance ophthalmic surgery.

iOCT is a tool that aids in our clinical understanding of pathophysiology otherwise obscured due to poor visualization, and enabled surgeons to in vivo study their practice patterns, achieving a greater understanding of the surgical interventions and their respective tissue alterations [20, 21]. Nevertheless the current body of research consists of low level evidence studies as the majority of studies consist of case reports/series and pilot studies. Moreover, a lot of studies lack objective measurable outcomes and are therefore poorly comparable. This is a major limitation of this review, as it is difficult to objectively quantify the putative benefits of iOCT. In addition, large studies to date focus mainly on the perceived benefits of the surgeon. Perceived benefits from a patient's perspective should arguably be addressed more in future iOCT research.

Admittedly, iOCT itself has inherent limitations that limit its effectiveness and utility. First, acquisition of an iOCT platform represents a significant investment for most practices. Second, iOCT is a supplementary tool and the presence of the iOCT is not essential to safely performing the surgery itself. Current use of iOCT provides surgeons with new insights and evidence shows this improves surgical management and safety; in particular the detection of complications and if possible treatment. However, it remains debatable if the use of iOCT directly leads to significantly better postoperative outcomes in routine procedures, because most studies lacked a control group or did not find significant differences in postoperative outcomes. This does not mean that altered surgical decision making using iOCT has not improved outcomes for individual patients, but it is unclear to which extend iOCT improves surgical outcomes for the general patient. Third, current methods for manually reviewing the OCT image are inefficient; thus, information that could improve surgical outcome cannot be processed easily by the surgeon [12]. Integrating of tools for automatic information processing and clinical decision aids will increase the efficacy of iOCT, possibly rendering manual reviewing obsolete. Several groups have investigated and/or developed promising algorithms for; macular hole closure [65] or analyses of donor-recipient interface in posterior lamellar keratoplasty [85, 86, 133]. The use of augmented reality and the application of an stereoscopic OCT interface should be explored [9]. Augmented reality environments may improve the transmission of information, providing the surgeon with – at that moment the most – essential information [134]. The implementation of stereoscopic OCT opens up a new dimension and the volumetric data may be invaluable for future clinical tools [9, 133].

Two major technical limitations of iOCT should be addressed. All OCT technology is limited in the scanning speed and spatial resolution. Most iOCT platforms in use are spectral-domain OCT's with an acquisition speed of ~30.000 A-scan per second, limiting the amount and quality of B-scans that can be made within a reasonable timeframe [3]. Real-time visualization of tissue manipulation requires higher a-scan rates and/or more compact scan area's [135]. The use of swept-source OCT intraoperatively could mitigate this limitation. The unprecedented high rate of A-scans per second of swept-source OCT can significantly improve image quality, acquisition speed, and therefore the effectiveness in live imaging of tissue manipulation or interventions [136]. Moreover, swept-source OCT technology uses an 1050 nm wavelength, which has an improved penetrating depth, aiding the use of iOCT in glaucoma surgery. The other technical limitations is most difficult to mitigate; the inability – or with considerable loss of resolution – of OCT to scan through non-transparent, opaque, or cloudy tissue, as shown by the inability to visualize thin and small structures through clouded media [103].

Frequently encountered limitations and operational hurdles in iOCT is the learning curve and ease of use. The iOCT systems can be difficult to operate and are therefore time-consuming, particularly in the case of certain types of glaucoma and vitreoretinal surgery. Targeting and focusing the iOCT image may be aided by implementation of image tracking and autofocus options. In addition, the use of metallic instruments or other non-transparent tools can obscure the surgeon's actions and cast a shadow on the tissue. However, suitable IR-transparent and iOCT-compatible instruments have been tested and will likely be available in the near future, although these instruments result in significant investments next to the iOCT-platform [12].

Lastly, advances in iOCT may also facilitated the development of robotic surgical systems, and we expect iOCT to reach its full potential in this field. For example, iOCT can aid navigation and provide direct feedback to the surgical robot as is already shown in the in vivo distance measurements of the Preceyes' ophthalmic surgical robot platform [137, 138].

In summary, iOCT is a promising new advancement in ophthalmic surgery with the ability to revolutionize ophthalmic surgery and improve treatment outcomes. Though adaption barriers and technical limitations need to be addressed. Ideally, future iOCT platforms should have a modular design, have image tracking and autofocus or able to handle voice-activated controls, and offer extensive review capabilities, with the ability to integrate automated image-analysis tools and compatibility with robotic surgical systems.

SUMMARY

What was known before

- Intraoperative OCT provides the surgeon with in-depth, real-time visual feedback during surgery.

- Intraoperative OCT enables new modalities for surgical decision-making and may lead surgical safety and efficiency.

What this review adds

- This review provides a comprehensive overview of the current clinical applications of intraoperative OCT and putative benefits.
- Intraoperative OCT imaging provides opportunities for the development of novel surgical procedures/tools, and stimulates evidence-based medicine.
- Technical and operational hurdles limit the adoption and utility of intraoperative OCT.

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AUTHOR CONTRIBUTIONS
MBM was responsible for design of the review protocol, writing the report, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, updating reference lists and creating'Summary of findings' tables. RPLW was responsible for design of the review protocol, and contributed to writing the report, arbitrating potentially eligible studies, and critical revision of the report. PAWJS, HJMB, JHdB, SMI, provided feedback on the report.

COMPETING INTERESTS
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