DIPLOMA THESIS

THERAPY OPTIONS AFTER FAILED TRABECULECTOMY

Submitted by

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AFFIDAVIT

I declare on my honour that I have written this thesis on my own and without external help. Furthermore, I declare that I have not used any other sources than the ones cited and that all the text passages that are quoted from these sources, either in terms of content or verbatim, are marked.

Graz, January 2017

Alexander Steinmaurer eh.

ACKNOWLEDGEMENT

At the very first, I honestly want to thank my parents for all the provided support during my years of study. I am truly grateful for their open-minded attitude and their focus on and their appreciation for good education that has inspired me to work hard. I am thankful that they have given me the chance to attend university, in particular, to study medicine and to spend some elective placements abroad.

Furthermore, I want to thank my first mentor, Christoph Faschinger, MD, PhD for the excellent supervision during the development process. His willingness to mentor me enabled me to write this diploma thesis at the eye clinic, to gain a deeper understanding of the glaucoma and will have finally helped me to achieve what I have always wanted so much: He will have helped me to take the first hurdle on the road to becoming an ophthalmologist.

CONTENT

ACRONYMS

ABC	Ahmed Baerveldt Comparison Study
ALT	Argon laser trabeculoplasty
AVB	Ahmed versus Baerveldt Study
DLT	Diode laser trabeculoplasty
ECP	Endoscopic cyclophotocoagulation
5-FU	5-Fluorouracil
IOP	Intraocular pressure
MLT	Micropulse laser trabeculoplasty
MMC	Mitomycin C
Nd:YAG	Neodymium: Yttrium-Aluminium-Garnet-Laser
SLT	Selective laser trabeculoplasty
TCP	Transscleral cyclophotocoagulation
TVT	Tube versus Trabeculectomy Study

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ABSTRACT

Purpose: After trabeculectomy, too excessive wound healing is unwanted because it increases the conjunctival resistance and therefore causes bleb failure. However, often it cannot be suppressed sufficiently and if bleb failure is refractory to treatment, what means that the failure of primary trabeculectomy is confirmed and irreversible, further treatment options need to be considered. It is the intention behind this essay to discuss and to compare these treatment options for the chronic open-angle glaucoma. However, prior to discussing the treatment options after failed trabeculectomy, the options that are available to target bleb failure should be presented and studied closely.

Methods: All the sources that have either been used to develop the basic structure of this essay or to write it are papers or well-known ophthalmologic reference books. The papers that are of high relevance for this topic could have been identified by searching *PubMed*.

Results: Prior to further surgery, it may be useful to restart or to intensify medical treatment and to take advantage of laser interventions. Laser trabeculoplasty or cyclophotocoagulation may be the options of choice. All in all, cyclophotocoagulation has a higher pressure lowering impact, but the complication profile is more severe as well. Further surgery is indicated if glaucoma is refractory to medical and laser treatment or primarily if the surgical approach has been taken. After failed trabeculectomy, all kinds of surgery are still possible, but due to its better safety profile, tube shunt surgery might be beneficial to further trabeculectomy. The different tube shunts appear to have a similar impact on IOP, but the size of the tube shunt does seem to be of importance. The role of mini-tube shunt surgery is still discussed controversially because the extent of its IOP reduction remains unclear, but it seems to be comparable with the one after trabeculectomy. The pressure lowering impact of non-penetrating surgery is considered to be a bit lower than the one of penetrating surgery, but nevertheless, it is a promising intervention, especially due to its great safety profile.

Conclusion: Glaucoma therapy is characterised by its very high number of different treatment options and this variety explains why that many treatment strategies are successful. Subsequently, the treatment concept needs to be coordinated with the individual situation

and its final success depends on the skills as well as on the professional experience of the treating ophthalmologist.

KURZFASSUNG

Zielsetzung: Nach erfolgter Trabekulektomie ist ein zu ausgeprägter Wundheilungsprozess unerwünscht, da dadurch der Abflusswiderstand in der Bindehaut steigt und zum Versagen des Filterkissens führt. Oft aber kann die einsetzende Wundheilung nicht ausreichend unterdrückt werden und sobald das Versagen des Filterkissens keinen weiteren therapeutischen Interventionen mehr zugänglich ist, ist das Versagen der primären Trabekulektomie bestätigt und irreversibel. Weitere Behandlungsoptionen müssen überlegt werden. Das Ziel dieser Arbeit ist die Diskussion und der Vergleich dieser Optionen für das chronische Offenwinkelglaukom. Aber zuvor sollen die verfügbaren Behandlungsmethoden bei versagendem Filterkissen präsentiert und im Detail beleuchtet werden.

Methoden: Die Quellen, die entweder zur Planung oder zur Erstellung der Arbeit herangezogen wurden, sind Papers oder bekannte ophthalmologische Nachschlagewerke. Die Papers, die für dieses Thema von besonderer Bedeutung sind, konnten via Literaturrecherche in *PubMed* gewonnen werden.

Ergebnisse: Vor weiteren chirurgischen Interventionen mag es sinnvoll sein, die medikamentöse Therapie wieder zu beginnen oder zu intensivieren und sich die Wirkung von Laserbehandlungen zu Nutzen zu machen. Die Trabekuloplastik oder die Zyklophotokoagulation mögen die Therapie der Wahl sein. Alles in allem senkt die Zyklophotokoagulation den Augeninnendruck stärker, hat aber auch ein schwerwiegenderes Komplikationsprofil. Weitere chirurgische Maßnahmen sind indiziert, wenn das Glaukom weder auf die medikamentöse Behandlung noch auf die Laserinterventionen anspricht oder primär, wenn der chirurgische Ansatz gewählt worden ist. Nach nicht mehr ausreichend funktionierender Trabekulektomie sind noch alle chirurgischen Interventionen möglich, aber die Implantation eines Tube-Shunts scheint ein besseres Sicherheitsprofil als eine weitere Trabekulektomie zu haben und mag daher vorteilhaft sein. Die verschiedenen Tube-Shunts haben eine vergleichbare drucksenkende Wirkung, wobei die Größe des implantierten Tube-Shunts von Bedeutung zu sein scheint. Die Rolle der Mini-Tube-Shunts bleibt umstritten, da das Ausmaß ihrer Drucksenkung unterschiedlich ist, aber diese scheint mit der nach Trabekulektomie vergleichbar zu sein. Die nicht-penetrierende Chirurgie mag, im Vergleich

zur penetrierenden Chirurgie, den Druck etwas schwächer senken, ist als nebenwirkungsarmer Eingriff aber trotzdem vielversprechend.

Fazit: Die Glaukomtherapie zeichnet sich durch eine besonders große Anzahl an verschiedenen Behandlungsoptionen aus und diese Vielfalt bedingt den Erfolg so viel verschiedener Behandlungsstrategien. Das Behandlungskonzept muss daher auf die individuelle Situation abgestimmt sein und dessen Erfolg ist letztendlich durch die Fertigkeiten und die klinische Erfahrung des/r behandelnden Ophthalmologen/in bedingt.

1 INTRODUCTION

Trabeculectomy is performed to lower intraocular pressure (IOP) by connecting the anterior chamber to the sub-Tenon's space, allowing the aqueous humour to flow out of the bulb through the created fistula. It was introduced in 1968 by Cairns on the basis of previous operation methods. Long before, in 1867, De Wecker initially had performed anterior sclerotomy. It had been the first surgical attempt to treat chronic glaucoma. The idea behind was simple and is exactly the same that underlies modern trabeculectomy: In order to increase aqueous drainage, De Wecker created an artificial outflow pathway through the sclera. For this purpose, he made a full thickness scleral incision 1mm posterior to the limbus. (1)

After more than 100 years, Cairns identified the trabecular meshwork as the leading cause for chronic open-angle glaucoma and intended to excise a block of Schlemm's canal and trabeculum. Due to the underlying technique this method was named trabeculectomy. However, creating a drainage bleb was found to have a more powerful impact on IOP reduction and hence, this technique was modified again. A filtration bleb was created and since then, trabeculectomy has been characterised by the filtration of aqueous humour. The name has stayed. (2)

Primary trabeculectomy is indicated if target IOP isn't reached on maximally tolerated medical treatment or after laser trabeculoplasty. In cases of noncompliance, advanced visual-field defects and rapidly progressive visual-field loss trabeculectomy might be indicated earlier. (2)

Khaw et al. declare trabeculectomy to be the "'gold standard' GFS (glaucoma filtration surgery) for many types of glaucoma"(2) in their review printed in "Albert & Jakobiec's Principles and Practice of Ophtalmology". Nowadays, trabeculectomy is still the most common primary surgical procedure. However, indication for trabeculectomy needs to be reflected carefully because trabeculectomy tends to fail after some time. The success of trabeculectomy is limited for most patients.

The Tube versus Trabeculectomy Study (TVT) is the most relevant trial in which different options for secondary surgical procedures have been compared. The results of the currently up-coming and very promising tube shunt surgery were compared to the ones of trabeculectomy. A highly relevant setting for clinical practice. Patients that were enrolled in

this study were between 18 to 85 years old, had previous trabeculectomy, cataract extraction with intraocular lens implantation or both and had inadequately controlled glaucoma on tolerated medical therapy. (3) The period between previous surgery and surgical treatment in the study (57 months ± 52) (3) serves as an indicator for the endurance of success (of primary trabeculectomy). The mean is 57 months. From this it follows that 50% of all the patients were re-operated within 57 months, so within 4 years and 9 months. Ninety percent[1] of the patients, so nearly all of them, were re-operated within 10 years and 4 months.
These data are not too promising and prove that success of trabeculectomy is limited. You may conclude that although primary trabeculectomy is necessary for many patients, it should - in order to achieve long term success – only be performed if other therapy options appear to be ineffective. Still, many therapy options are available after failed trabeculectomy, but their success is not of unlimited extent either. Good timing is of importance for long-lasting success. The moment when decision for primary trabeculectomy is made in the course of glaucomatous progression might function as a sort of key point in the treatment process.
Most patients, whose primary trabeculectomy has already failed, are at an advanced stage. Reasons for failure are different. It is caused either if trabeculectomy fails or if glaucoma progresses.

In this review, the therapy options after failed trabeculectomy should be discussed for the chronic open-angle glaucoma. My approach to this topic has necessarily been formed by the following line of thought: Prior to considering further treatment, failure of trabeculectomy needs to be confirmed. Different interventions, like needling and the application of antimetabolites, have been developed to recreate, if drainage has once stopped, the fistula that has been failed. These potential interventions should be presented and discussed primarily (chapter 2). If bleb failure is finally confirmed, the patient needs to decide together with the doctor for one of the three treatment columns in glaucoma therapy: Medical treatment, laser treatment and surgery. In most cases, the patient will have already been treated by medication and laser before primary trabeculectomy, but medical therapy could have been reduced or stopped after surgery due to the surgical success. According to the risks of surgery and the time-limited effect, which I have already illustrated above, it makes sense in many situations to take the whole potential benefit from medical and laser treatment before deciding for further surgery. However, I need to emphasise from the very beginning that, although surgery will mostly be the last column used in antiglaucoma treatment, the

[1] $(x - 57) / 52 = 1{,}2816 \rightarrow x = 124$

treatment columns are not ranked and that the order depends on the individual patient and the individual situation.

After providing a short overview of the glaucomatous diseases in the second part of this introductory chapter, in chapter 1.1, including its definition, its classification and aetiology as well as the treatment principles, and after presenting and discussing the interventions to treat bleb failure in chapter 2, I am going to deal in chapter 3, entitled "How to maintain the success of primary trabeculectomy after irreversible bleb failure", with the medical and laser treatment options. Although medical and laser treatment options are separate treatment columns, they shall be discussed together, because they need to be considered before surgery. In my point of view, further medical treatment as well as further laser treatment can mostly be seen as prolongation of the primary surgical success (non-surgical approach), because very often surgery is only indicated once more if medical and laser treatment is not practicable anymore, or at least if these treatment options have been considered again. Success of primary trabeculectomy is prolonged by medical and laser treatment, especially according to the fact, that the medical and the laser treatment column will have already been used prior to primary trabeculectomy.

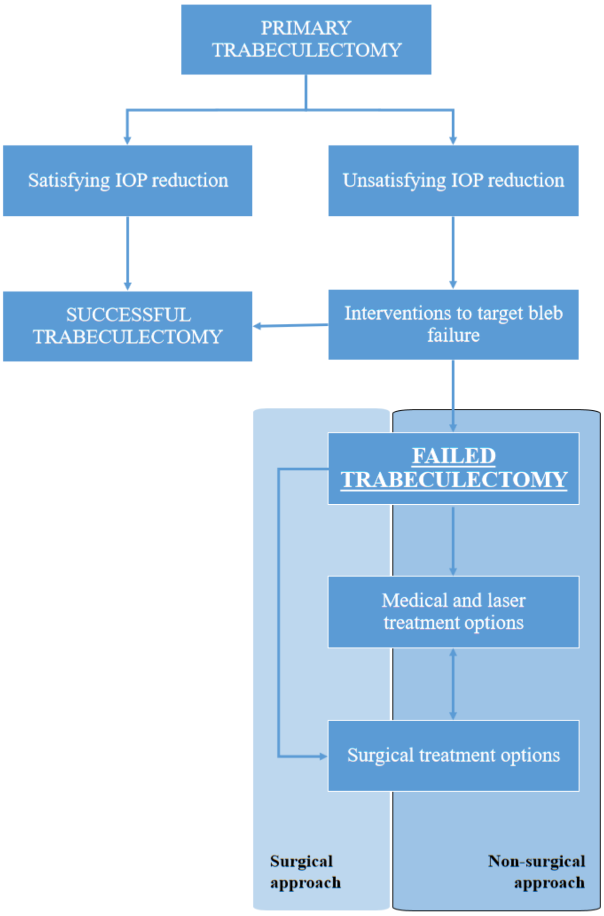

Figure 1: Different approaches in glaucoma therapy. This essay is structured upon the non-surgical approach. The situations in which the surgical approach should be favoured are discussed in subchapter 4.3.3.

The other approach, the surgical one, would be that surgery is not subordinated to medical and laser treatment in general and that the failure of these treatment options is not a general condition to consider further surgery. Subsequently, this second approach would mean that surgery is the favoured treatment option after failed trabeculectomy.

To me, the first one, the non-surgical approach, is the most conceivable approach and it is also the most frequently applied one and therefore, the medical and laser treatment options are discussed together prior to the surgical treatment options in chapter 4.

Each chapter, chapter 2 "How to target bleb failure", chapter 3 "How to maintain the success of primary trabeculectomy after irreversible bleb failure", as well as chapter 4 "Indication for further surgery" are divided into the subchapter x.1 "Different treatment options", where the treatment options are presented and described, including their complication rates and contraindications, followed by the subchapter x.2 "Results", where the most important study results are presented in order to prepare the data for the ongoing discussion in the subchapter x.3 "Discussion", where the indication for the individual treatment options should finally be worked out.

In the last subchapter of chapter 4, chapter 4.3.3, the surgical and the non-surgical procedures should finally be compared directly and should be discussed on the basis of the surgical approach. The conditions under which surgery should be prioritised, even if medical and laser treatment options have not been exhausted, should be discussed.

My final statement is presented in chapter 5 "Conclusion".

All the sources that have either been used to develop the basic structure of this essay or to write it are papers or well-known ophthalmologic reference books. The papers that are of high relevance for this topic could have been identified by searching *PubMed*.

1.1 Glaucoma – A family of eye diseases characterised by the degeneration of the optic nerve

1.1.1 Definition

„Glaucoma“ is a collective term for different eye diseases that share some common characteristics. It’s difficult to find the only and exact definition, because definitions do vary from author to author, each one seems to emphasise slightly different elements in his definition. To introduce in this review, I’m primarily going to work out the definition on my own:

Glaucoma (4): Optic neuropathy with a characteristic pathologic appearance of the optic disc. It results in characteristic scotoma and develops due to an individually too high intraocular pressure (IOP).

- Ad “individually too high intraocular pressure (IOP)”: The IOP is determined by the production of aqueous humour as well as on the capacity of its two outflow pathways. The most important one is the Schlemm’s canal but also uveoscleral drainage needs to be mentioned. The pressure damages the retinal nerve fibres of the retinal ganglion cells, but IOP is not the only risk factor, the extent of cell death depends on the pressure level as well as on the constitution of the retina. Weak nerve fibres are more liable to loose their function, while strong ones are more resistant to IOP and damage. Finally, glaucoma is caused if a certain proportion of IOP and retinal constitution is exceeded. The critical IOP value above which glaucoma develops depends on the individual constitution of the retina, but only IOP can be measured quantitatively. Glaucoma is called normal-tension or low-tension glaucoma if the critical IOP is lower than the maximum IOP of the healthy population. The other way round, if the IOP of a healthy individual is higher than the maximum IOP of the healthy population and even though the individual does not develop glaucoma, the elevated IOP is described best by the term "ocular hypertension". (5)

- Ad "characteristic pathologic appearance of the optic disc": High IOP leads to the destruction of retinal nerve fibres resulting in an atrophy of the optic nerve. Subsequently the cup of the optic disc grows. The ratio between the diameter of the cup and the diameter of the disc indicates, if a certain reference value is exceeded, the presence of glaucoma. The vertical diameters are taken for consistent approach and those ratio should not exceed 0,65. Helpful might be the difference in the ratio between both eyes, a difference of more than 0,2 is highly suspicious for glaucoma. Most discs obey the ISNT-rule, what means that the neuroretinal rim is largest at the inferior pole, followed by the superior, the nasal and the temporal pole. However, one single observation does not guarantee the diagnosis. Diagnosis is only confirmed if the cup increases constantly in size. One differential diagnosis of the glaucoma is the macro-papilla, a normal variant of the disc, which is constant in size and does not cause vision loss. In case of glaucoma, the progression of the atrophy can be monitored by the "Optical coherence tomography (OCT)" and the "Heidelberg Retinal Tomograph". (5)

  Differential diagnoses of the degeneration of the optic disc include neuritis nervi optici, papilledema due to elevated brain pressure and anterior ischemic optic neuropathy. In contrast to glaucoma, they primarily cause papilledema that finally results in optic atrophy. (6)

- Ad "characteristic scotoma": As the optic disc is located nearly in the centre of the fundus, the nerve fibres deriving from the periphery need to be longer than the ones located next to the optic disc.

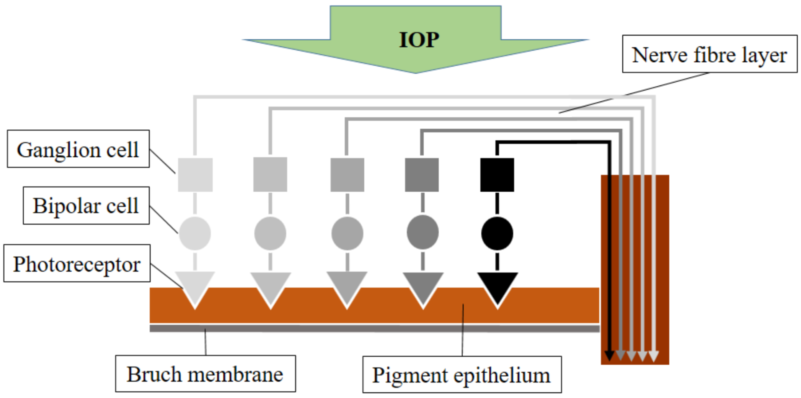

Figure 2: Arrangement of the nerve fibres. The darkness increases with the protection from the nerve fibre layer.

  Subsequently the thickness of the retinal nerve layer, that protects the underlying photoreceptors, decreases with the distance from the disc. This is the reason why scotoma typically starts in the periphery and continues to spread towards the cup. Subsequently it remains undetected by the patient for a long time. (7)

1.1.2 Classification and aetiology

The open-angle glaucoma needs to be distinguished from the angle-closure glaucoma. The term “angle” refers to the iridocorneal angle. Subsequently the angle-closure glaucoma is defined by the protrusion of the iris into the angle, while the open-angle glaucoma is characterised by the physiological morphology of the chamber angle. (4)

Both types of glaucoma might occur primarily, if they occur in a predisposed eye without any other ocular or systemic factor, or secondarily. Apart from this classification, the glaucoma can be congenital or acquired. (4)

This essay does deal with the acquired forms of open-angle glaucoma only.

In open-angle glaucoma the chamber angle is not blocked by the iris. In contrast, “angle-closure” refers to the block of the chamber angle by the iris. (4)

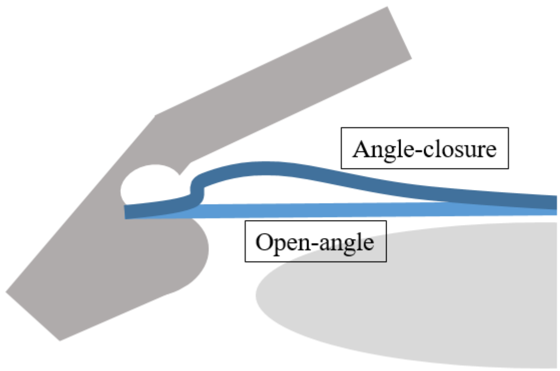

Figure 3: Open-angle and angle-closure

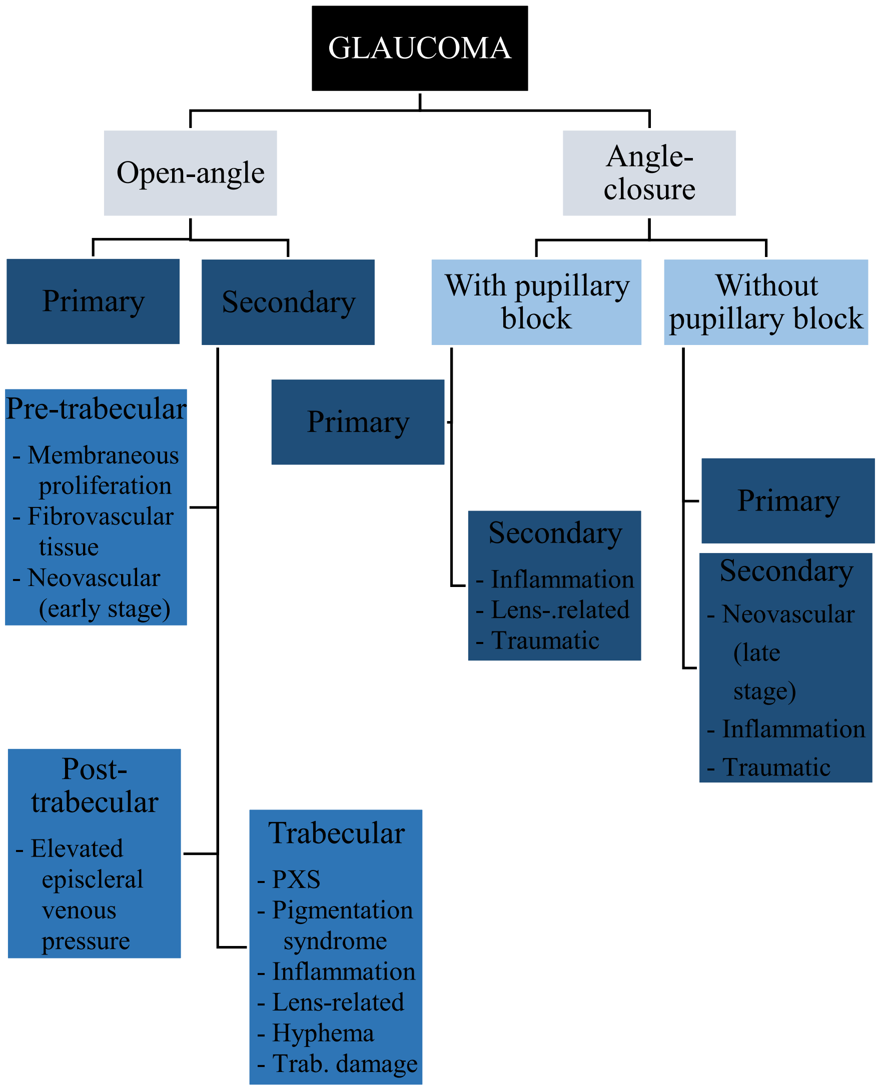

Figure 4: Classification of the glaucomas

Classification by the type of onset/origin

Subtypes of primary glaucoma (5): No ocular or systemic risk factors are present.

- Primary open-angle glaucoma: Caused by the degeneration of the trabecular meshwork. Makes up 90% of all glaucomatic diseases and commonly affects both eyes in different severity levels.
- Primary angle-closure glaucoma
  - With pupillary block: High resistance between the iris and the lens increases IOP behind the iris and results in its protrusion that blocks the angle. Mydriasis is a common risk factor. Glaucoma is the consequence of the persistent angle-closure syndrome.

- Without pupillary block: Caused by the occurrence of a plateau iris, or if the iris is thicker and positioned more anteriorly.

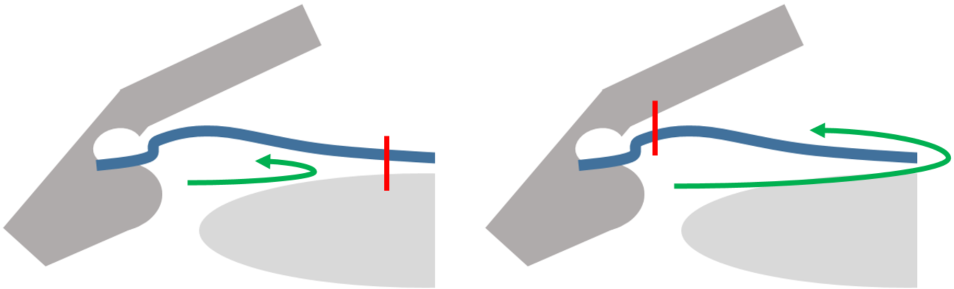

Figure 5: Angle-closure with and without pupillary block.

Subtypes of secondary glaucoma (5): Ocular or systemic risk factors are present.

- Pseudoexfoliation glaucoma due to the pseudoexfoliation syndrome: Pseudoexfoliative material (PXF) is a grey-white fibrillary amyloid-like substance from pathologic processes in the extracellular matrix that is deposited in the anterior segment of the eye. Especially women older than 50 years are effected.
  - = Trabecular open-angle glaucoma
- Pigment dispersion glaucoma due to the pigment dispersion syndrome: Pigment granules from the iris pigment epithelium are deposited mostly in the anterior segment of the eye. Especially young myopic white man are effected.
  - = Trabecular open-angle glaucoma
- Neovascular glaucoma due to rubeosis iridis, mainly caused by chronic retinal ischaemia: Vascular endothelial growth factor (VEGF) and other angiogenic factors trigger vascularisation on the iris.
  - = Angle-closure glaucoma without pupillary block in the late stage. Pre-trabecular open-angle glaucoma in the early stage.
- Inflammatory glaucoma due to intraocular inflammation, mostly chronic anterior uveitis and Fuchs uveitis syndrome.
  - = Angle-closure with pupillary block due to synechiae (seclusio pupillae)
  - = Angle-closure without pupillary block or trabecular open-angle glaucoma due to deposition of debris that may pull the iris forward or just blocks the outflow pathway.
- Lens-related glaucoma:
  - = Trabecular open-angle glaucoma: High molecular-weight lens proteins block the trabecular meshwork in case of hypermature cataract.

    - = Angle-closure with pupillary block due to an increase of the lens in size or due to disruption from the lens positon.
- Traumatic glaucoma
    - = Trabecular open-angle glaucoma due to hyphema or scaring.
    - = Due to angle recession or trabecular damage.
- Steroid-induced glaucoma
    - = Trabecular open-angle glaucoma due to disposal of mucopolysaccharides.
- …

Classification by the type of temporal behaviour

Primary open-angle glaucoma is a chronic disease, the damage to optic nerve occurs slowly. "Acute" forms do exist of the secondary open-angle glaucoma, like in case of trabecular block by the deposition of debris during an episode of acute uveitis.
Angle-closure glaucoma is generally characterised by faster progression and sometimes also by an acute onset. The preceding angle-closure syndrome goes along with an IOP multiple higher than in chronic open-angle glaucoma. Damage to the optic nerve occurs soon if the angle-closure syndrome is not treated promptly. However, also chronic forms exist.

This essay deals with the chronic open-angle glaucoma.

1.1.3 Treatment principles

In general, treatment is matched with symptoms and clinical parameters. In case of chronic open-angle glaucoma, the only symptom is loss in visual field, called scotoma. It manifests at the late stage of the disease and does only proceed slowly. Also the pathologic appearance of the disc develops that slowly. The detection of an increased excavation is necessary for the definite diagnosis of the glaucoma but the development of the disc is only suitable to check the treatment effect if monitored by OCT or HRT. The only option is to treat IOP, although everyone should be aware that IOP is only a factor that triggers glaucoma. In general, doctors are told to treat humans with special attention to his or her demands rather than diseases and clinical parameters. However, for glaucoma, regulation of the IOP is the best option. It's necessary to mention that the actual "intra"-ocular pressure is often lower than the measured pressure. This deviation depends on the corneal thickness, as IOP is measured from extrabulbar. To estimate and to adjust IOP, the corneal thickness needs to be measured by pachymetry.

Glaucoma therapy consists of three treatment columns: Medical treatment (1), laser treatment (2) and surgery (3). All three groups are still of importance after failed trabeculectomy. The therapy options after failed trabeculectomy are complemented by specific interventions which shall be presented and discussed in chapter 3.

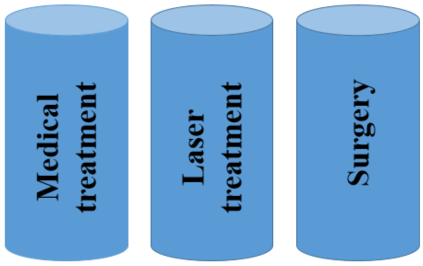

Figure 6: Treatment columns of glaucoma therapy

The goal of the treatment is IOP reduction. Aqueous outflow needs to be higher than its production. The way this goal is achieved doesn't matter. Aqueous production might be inhibited or any resistance that keeps aqueous outflow low might be eliminated. For the definite aqueous outflow, the resistance of the whole pathway matters and this one is defined by the sum of all single resistances. The manipulation of a specific, the causal and aetiological resistance is often not important and might be replaced by the manipulation of a different one or different ones, as long as the total reduction remains the same.

However, IOP reduction should not be too high either. Persistent hypotony is a serious complication after surgical procedures. Long-termed, aqueous production needs to be exactly the same like aqueous outflow. This principle might be visualised by the image of a scale.

2 HOW TO TARGET BLEB FAILURE

2.1 Treatment options

This chapter is limited to interventions that lower IOP. The term "bleb failure" indicates that IOP reduction is unsatisfyingly low and does not include pathologies that result in postoperative hypotony.
Laser suture lysis and Nd:YAG goniopuncture are not presented in this chapter but due to their specific indication for the treatment of bleb failure in the general one of laser treatment.

One remarkable side effect of all interventions targeting bleb failure is hypotony. It occurs if the procedure is timed wrongly or if application lasts too long what means that the intended IOP-lowering effect turns out to be too dominant. The only procedure, that cannot result, due to its soft nature, in hypotony, is bleb massage.
After each procedure (apart from bleb message), antiphlogistic eye drops are indicated.

a) Bleb massage: Digital pressure is exerted posterior to the flap. It is carried out until a functioning bleb forms and may be repeated several times during the first weeks. (2)

b) Scleral flap suture manipulation: One or more stitches are either removed by cutting them through or are lysed by an argon or diode laser, that leaves the conjunctiva untouched. The number of stitches being opened and the timing may influence the outcome and is discussed in chapter 2.3. (2) (8)
Possible complications are postoperative inflammation and subconjunctival haemorrhage. In some cases, if the Tenon's capsule is quite thick, suture manipulation won't be successful. (9) The removal of releasable sutures includes corneal damage as a further complication.

c) Subconjunctival application of antimetabolites: Antimetabolites are drugs that inhibit the proliferation of the conjunctiva and the Tenon's capsule and also slightly of the sclera.

Most patients receive them intraoperatively, but in case of bleb failure, further postoperative application is recommended. While Mitomycin C (MMC) and 5-Fluorouracil (5-FU) are in use during surgery with MMC being the more frequently used agent, 5-FU is due to its less aggressive behaviour the more frequently used agent in the postoperative setting. The 5-FU series are shaped differently; each clinic has its own intervals, but the common time frame is confined between the first postoperative week and several months. (2) (10) In Graz, 5-FU is usually injected daily for a period of 5 days and the series may be repeated.

d) Bleb needling: Bleb needling is either performed of the Tenon's capsule or of the scleral flap. After the application of topical anaesthesia and of a vasoconstrictive agent, a needle is stuck through the conjunctiva near the fornix, is gently pushed forward to the posterior margin of the trabeculectomy and finally the margin is stuck several times until the size of the bleb increases. Seldom it may also be performed via the anterior chamber and may include the injection of viscoelastic material or may be continued under the scleral flap. (2)

e) Nd:YAG laser goniopuncture: Commonly used after failed non-penetrating surgery in order to break the integrity of the trabeculo-Descemet's membrane and to convert it to a penetrating procedure, Nd:YAG laser goniopuncture has also become important for the treatment of late bleb failure. Via gonioscopy, the laser is aimed at the deepest point of the ostium and 10 to 20 shots are applied. After gonioscopy, a bleb should form. (11)

2.2 Results

Scleral flap suture manipulation

Ramakrishna et al.: Study of efficacy and timing of laser suture lysis in reducing intraocular pressure after trabeculectomy with mitomycin-C (12): 352 patients

Table 1: Results from Ramakrishna et al.	Suture lysis … after trabeculectomy			
	within the first 3 weeks	within the 3rd and the 5th week	after the 5th week	p-Value
IOP before suture lysis (mean +- SD, mmHg)	20,0 +- 3,9	20,4 +- 5,7	21,6 +- 9,5	0,803
IOP immediately after suture lysis (mean +- SD, mmHg)	11,1 +- 4,0	15,8 +- 6,0	18,3 +- 8,8	**0,047**
IOP after a follow-up of 1 week (mean +- SD, mmHg)	12,5 +- 4,7	15,8 +- 5,5	16,7 +- 5,6	0,204
IOP after a follow-up of 6 months (mean +- SD, mmHg)	13,5 +- 1,9	13,5 +- 3,1	14,6 +- 4,0	0,476

“Complications such as shallow anterior chamber and hypotony occurred in 3 (0.04%) eyes in the subgroup wherein laser suture lysis was performed earlier than 3 weeks posttrabeculectomy.”

Krömer at al.: Laser suture lysis after trabeculectomy with mitomycin C: analysis of suture selection (13): 120 patients

Table 2: Results from Krömer et al.	Mean IOP reduction (mean +- SD, mmHg)
Suture lysis performed within 7 days after trabecuelctomy	6,3 +- 6,9
Suture lysis performed later than 7 days after trabecuelctomy	7,0 +- 5,1

These two trials are in contradiction to each other.

Application of antimetabolites, Needling

Due to the large number of published trials and their varying results, no results are presented in this subchapter. For the discussion see chapter 2.3.

Nd:YAG laser goniopuncture

Susanna Jr et al.: Nd:YAG Laser Goniopuncture for Late Bleb Failure After Trabeculectomy With Adjunctive Mitomycin C (11): 19 patients.

Table 3: Results from Susanna Jr et al., 6 months follow-up		p-Value
Decrease in IOP: Goniopuncture was performed 35,7 +- 32,3 months after trabeculectomy. (mean +- SD, mmHg)	20,9 +- 4,5 to 11,9 +- 4,1	**< 0,001**

In eyes with late bleb failure, IOP decreased significantly after Nd:YAG goniopuncture.

2.3 Discussion

Which one is the best order to treat bleb failure? The order of presentation of the different treatment options in chapter 2.1 reflects the common proceeding, but it is not the only plausible way of targeting bleb failure. Hence, which modifications are possible?

The first intervention is always bleb massage. It is effective shortly after surgery and hardly shows side effects. It is very safe and hence an attempt should be made. However, effect is also limited. Often it is not successful and if it is successful, it may only last for short. (2)

The manipulation of the scleral flap sutures is the next step if bleb massage has failed. If the bleb doesn't form, it does make sense to reduce the tension of the flap by opening sutures. If aqueous humour cannot leave the bulb, a bleb will never form. Subsequently it does not make full sense to describe this pathological mechanism by the term "bleb failure", because the problem is not that the bleb does not work, it is that the bleb does not form itself, what means that the bleb does not exist. This incapability to form is caused by a too tight adherence of scleral flap to the scleral bed causing scleral resistance that is too high while bleb failure (in its true understanding) is caused by an increased conjunctival resistance. To allow a bleb to form, both resistances need to be matched to each other. Suture manipulation influences the scleral resistance only and subsequently it is not unlimitedly the next step after failed bleb massage. If a bleb has already formed and failure appears after many weeks post surgery, failure is associated with an increased conjunctival resistance, what points to conjunctival fibrosis. Then, the manipulation of the scleral flap sutures may not be the optimal approach because it targets the scleral resistance only. (14) (2)

The brand new study by Ramakrishna et al. (12) identified the optimal period for the manipulation of sutures after trabeculectomy with MMC to be between the third and the fifth week. Within the first weeks, the incidence for hypotony is higher and after the recommended period, the success rate goes down due to the advanced wound healing process. Krömer et al. (13) showed in a study after trabeculectomy with MMC that the sort of suture that was opened, whether it was a central or a corner suture, did not make any significant difference in IOP reduction. Furthermore, they could not report any correlation between the time of suture lysis and IOP reduction. However, these results are in contradiction to other results, like the ones, that have just been mentioned by Ramakrishna et al. (12), and to a similar trial carried out by Bardak et al. (15).

Releasable sutures are removed and fixed sutures are lysed like described in chapter 2.1. The expected IOP reduction is about 5mmHg. (12)

To avoid hypotony, it makes sense to open one suture after each other. Only if IOP remains increased, the next one should be cut.

If suture manipulation has failed too or if it has not been carried out because the bleb has not been suitable to, three options are left to recreate the function of the bleb: The administration of antimetabolites, the needling and the Nd:YAG laser goniopuncture.

The administration of 5-FU, the most common antimetabolite used postoperatively, is preferred for the treatment of early bleb failure while both other options are more suitable to treat late bleb failure. It is discussed controversially whether MMC may be indicated as well. It is more aggressive because it inhibits the proliferation of all cells it gets in contact with, while 5-FU inhibits cells that are in the synthesis phase of the cell cycle only. Some authors (2) reported an alarming complication profile of postoperative MMC with higher rates for hypotony, while, for example, Liu et al. (14) didn't find any difference in the complication rates between MMC and 5-FU compared with needling and could even prove a higher success rate for the MMC-group. In contrast to all the other possible interventions, antimetabolites mainly tackle the conjunctival resistance and inhibit conjunctival proliferation. Administration is indicated if conjunctival fibrosis limits the outflow and not if a bleb fails to form. In clinical practice, it's difficult to determine exactly the resistance that causes bleb failure. However, if bleb failure occurs early, if suture manipulation remains unsuccessful and if the conjunctiva appears to be thick, the conjunctival resistance is increased most probably. If prior interventions have failed to treat early bleb failure, 5-FU should be given as soon as possible because if it is administered too late, the IOP lowering effect will not be that dominant anymore. (2)

By needling and Nd:YAG laser goniopuncture, holes are sometimes made into the sclera and therefore the communication between the bleb and the anterior chamber is increased. Both interventions lower the scleral resistance and are therefore useful to treat late bleb failure. Needling additionally reduces the conjunctival resistance, at least for short, due to the stitch hole in the conjunctiva. The scleral resistance increases later than the conjunctival one because the scleral proliferation is slower and less strong (14), but of course, the type of failure can't be determined only by the point it occurs. The size, the height and the thickening of the bleb are important parameters as well. Needling and Nd:YAG laser goniopuncture are both effective and safe procedures, still recommended for late bleb failure. Needling is more successful if done sooner and if the bleb is big and high, at least in combination with the application of antimetabolites. (16) (14) I could not find direct comparison of needling and Nd:YAG laser goniopuncture, but they seem to be equally effective. (17) (11) (2)

3 HOW TO MAINTAIN THE SUCCESS OF PRIMARY TRABECULECTOMY AFTER IRREVERSIBLE BLEB FAILURE

3.1 Treatment options prior to further surgery

Like explained previously, the suspected failure of a filtering bleb needs to be confirmed prior to performing any treatment and if failure is confirmed, efforts need to be made to restore the function of the bleb (chapter 2). However, if bleb failure remains irreversible, two different approaches are possible for the further treatment: On the one hand, the non-surgical treatment options, medical and laser treatment, could be understood, like explained in the introductory chapter, as a prolongation of the primary surgical success, meaning that trabeculectomy has not failed until these options are exhausted and hence these treatment options could be favoured. On the other hand, surgery is not subordinated to medical and laser treatment in general and the failure of these treatment options is not the general condition to consider further surgery. Subsequently this second approach, the surgical approach, means that surgery is prioritised to medical and laser treatment. This chapter is built upon the non-surgical approach. Situations in which the surgical approach should be favoured are discussed in subchapter 4.3.3.

3.1.1 Medical treatment

The following groups are the 5 main ones for the topical treatment of the chronic open-angle glaucoma:

- Prostaglandin derivatives
- Beta-blockers
- Carbonic anhydrase inhibitors
- Miotics, Cholinergic agonists

- α2-Agonists

Table 4 should provide an overview of these groups and the most important side effects, without listening all of them in detail. The indications should be discussed in chapter 3.3.1.

The following ranking represents the maximal IOP drop after application. The data do vary from publication to publication but the ranking between the agents remains constant: (18)

1. 20-35% reduction: Prostaglandin derivates
2. 20-25% reduction: Beta-blockers, α2-agonists, miotics
3. 15-20% reduction: Topical carbonic anhydrase inhibitors

Table 4: Medication (19) (18) (20)	**Mechanism of action**	**Adverse drug events (Ocular and systemic)**	**Contraindications**	**Application, Onset of effect**
Prostaglandin derivates (Latanoprost, Travoprost, Tafluprost, Bimatoprost)	Increase in uveoscleral outflow. (Prostaglandin dilates blood vessels and activates metalloproteinases.) Increase in trabecular outflow is discussed as well.	Conjunctival hyperaemia, eyelash lengthening, hyperpigmentation of the iris and skin, … Systemic side effects are rare and harmless if existent.	Anterior inflammation	Once a day
Beta-blockers (Timolol (non-selective), Betaxolol (β1-selective))	Decrease in aqueous production	Hardly ocular side effects Systemic ones might be dangerous, like bronchospasm and the whole inhibiting impact on the cardiovascular system.	Bronchial asthma, COPD Cardiovascular diseases	1-2 times daily
Carbonic anhydrase inhibitors (Dorzolamid, Brinzolamid)	Decrease in aqueous production	Blurred vision, ocular paraesthesia, … Bitter taste, headache, …	Serious renal insufficiency	2-3 times daily
Miotics, cholinergic agonists (Pilocarpin, Carbachol)	Contraction of the ciliary muscle as well as miosis extends the trabecular meshwork. The elimination of the pupillary block is an additional effect for	Conjunctival hyperaemia, browache, lacrimation, local allergy, … Potential of dangerous systemic cholinergic side effects,	Anterior inflammation Secondary, lens related glaucoma	2-3 times daily

	the angle-closure syndrome/glaucoma.	especially if overdosed and headache, …		
α2-Agonists (Apraclonidin, Brimonidin)	Decrease in aqueous production Increase in uveoscleral outflow Neuroprotective effect is discussed as well.	Ocular events like stinging eyes and foreign body sensation (in case of allergic reaction), … Occasionally systemic events like tiredness, low blood pressure, sedation (especially for children), …	Therapy with oral monoamine oxidase inhibitors (risk of hypertensive crisis) and combination with other sympathomimetic drugs and tricyclic antidepressants	2 times daily

3.1.2 Laser treatment

Laser treatment is part of the standard management in the treatment of the open-angle glaucoma. Two types of laser treatment, trabeculoplasty and cyclophotocoagulation, are in use. Each method has its specific indications and side effects. For the treatment of the angle-closure syndrome/glaucoma, different interventions are in use, but they should not be presented in this essay as it is about the open-angle glaucoma only.

Laser, standing for "Light Amplification by Stimulated Emission of Radiation", is the simultaneous emission of electromagnetic waves on high intensity within a narrow frequency range. This simultaneous emission is triggered by the stimulation of light that exactly has the energy that is needed to beam an electron to the higher energy level. The energy released by passing again into the lower energy level is bundled to a laser beam. Lasers are made, like the Nd:YAG laser and the diode laser, out of solids or, like the argon laser, out of gases. The Nd:YAG laser uses a neodymium-doped YAG-crystal as laser medium and transmits infrared light and has its use, next to the medical application, in different technical fields, while the argon laser uses ionised noble gas argon to emit light. The core of the less frequently used diode laser is a semiconductor diode and hence, the electrons are beamed to the higher energy level by electricity. (21)

3.1.2.1 Laser trabeculoplasty

Trabeculoplasty lowers IOP by reducing the resistance of the natural outflow pathway. The laser beam is aimed at the trabecular meshwork and widens the canals. The exact mechanism is still unclear, but the effect seems to be caused by the destruction of cells and by a biologic response to the absorbed energy. (22)

Different wavelength are effective: (22) (5)

- Selective laser trabeculoplasty SLT is performed by the frequency doubled Nd:YAG laser. The treated area is, in comparison to the other forms, very big.
- Argon laser trabeculoplasty ALT is performed by an argon laser. The treated area is small and the laser is aimed at the anterior trabecular meshwork.

- Diode laser trabeculoplasty DLT is performed by a diode laser. The treated area is twice as big as in case of ALT but by far not that big as in case of SLT. The laser is either aimed at the anterior trabecular meshwork.

Table 5 provides the characteristics of the different forms:

Table 5: Laser types and their technical features (22)	**SLT**	**ALT**	**DLT**
Laser Power (mW)	270000000	1200	1400
Spot size (µm)	**400**	**50**	**100**
Duration (s)	0,000000003	0,1	0,2
Total energy (J)	**0,0008**	**0,1**	**0,3**
Total energy per µm (J)	**0,000002**	**0,002**	**0,003**
Placement	Pigmented TM	Anterior TM	Anterior TM
Number of burns (over 180°)	50	50	50

The three different laser types need to be compared according to their technical features. Some differences seem to be of special importance for the ongoing discussion:

- The total energy released is the lowest for SLT and the highest for the treatment with the diode laser. The argon laser is ranked in between.
- If the focus of attention shifts to the total energy per µm, the SLT remains at the lowest position, releasing 0,5µJ compared to the argon and the diode laser, releasing 2-3mJ.

Complications (22)

- Elevated IOP: IOP spikes are detected mostly about one hour after the intervention although they may also present later. After ALT, about 50 percent of the patients are affected. For SLT, the incidence is much lower. The main risk factor for IOP spikes is the level of pigmentation of the trabecular meshwork.

  IOP spikes are treated with IOP lowering drugs. Apraclonidine or brimonidine shortly before and after the procedure should prevent from IOP spikes. (23) Steroids are not effective.
- Decrease in visual acuity: Is either irreversible and results from ganglion cell death or regresses spontaneously.
- Macula edema
- Corneal edema

- Hyphema: Is an uncommon side effect and can be controlled by applying pressure via the contact lens.
- Discomfort
- Anterior uveitis and peripheral anterior synechia: The rate of inflammation is higher after SLT than after ALT. (24)

3.1.2.2 Cyclophotocoagulation

The idea behind cyclophotocoagulation is the partial destruction of the secretory ciliary epithelium. In contrast to laser trabeculoplasty, the outflow pathway remains unaffected and the aqueous production is limited.
Two forms are distinguished: (25) (26)

- Transscleral cyclophotocoagulation TCP: It is usually performed with the Nd:YAG laser and only seldom with a diode laser. The contact form needs to be distinguished from the noncontact form. For the noncontact method, the patient is positioned behind the slit lamp where the laser is located and the ophthalmologist targets the ciliary body by turning the laser beam. It should pass the sclera 1-1,5mm behind the limbus. About 32 spots are usually applied. For the contact method, the ophthalmologist places a probe on the conjunctiva 1-2mm posterior to the limbus and transmission is applied directly from this probe. 16-28 spots are set.
- Endoscopic cyclophotocoagulation ECP: A probe that includes the diode laser, a light source, an aiming beam, a fibre optic and a camera is inserted into the bulb. A paracentesis is made most commonly at the limbus because there is no risk for choroidal and retinal detachment, but the pars plana might be chosen alternatively. Two incisions are necessary to reach all ciliary processes. Only raised processes are of interest and energy is applied until they are destructed.

Complications: All the complications listed for trabeculoplasty are potential complications of cyclophotocoagulation as well. Additional complications for cyclophotocoagulation are: (27)

- Hypotony
- Phthisis bulbi
- Sympathetic ophthalmia

- Intraocular disruption (“pop”)
- Cataract
- Vitreal hemorrhage

Additional complications for TCP only are: (25)

- Conjunctival surface burns

Additional complications for ECP only, especially in phakic eyes, are: (25)

- Damage to the crystalline lens, zonular rupture
- Retinal detachment
- Endophthalmitis

3.2 Results

The results of important trials cited in the ongoing discussion are provided in this chapter. I need to emphasise that the selection of the papers has been made according to their impact and their suitability and is without any claim to completeness. The most suitable ones are provided exemplarily for the whole literature.

3.2.1 Laser treatment

3.2.1.1 Laser trabeculoplasty

SLT versus ALT versus diode

Bovell et al.: Long term effects on the lowering of intraocular pressure: selective laser or argon laser trabeculoplasty? (28): 152 patients

Table 6: Results from Bovell et al.	SLT	ALT
IOP reduction in 3 years (mean +- SD, mmHg)	6,7 +- 7,1	6,1 +- 5,1
IOP reduction in 4 years (mean +- SD, mmHg)	7,0 +- 7,7	6,3 +- 5,0
IOP reduction in 5 years (mean +- SD, mmHg)	7,4 +- 7,3	6,7 +- 6,6

„There was no statistically significant change in IOP in either of the two groups.”

Mc Alinden studied, in his review published in 2014, 17 papers, that compare SLT to other treatment modalities and concluded that there is no difference in IOP reduction between SLT and ALT. (29) Moreover, he believes that efficiency of 180° and 360° SLT is the same.

Repeated trabeculoplasty

Hong et al.: Repeat Selective Laser Trabeculoplasty (30): 35 patients (retrospective)

Table 7: Results from Hong et al.	**SLT 1**	**SLT 2**	**p-Value**
IOP change after 1-4 weeks (mmHg)	3,1	2,6	0,61
IOP change after 1-3 months (mmHg)	5,0	2,9	**0,002**
IOP change after 5-8 months (mmHg)	4,0	2,9	0,16

„Our findings suggest that repeat 360° SLT may be safe and effective after an initially successful 360° SLT has failed."

Laser trabeculoplasty after failed trabeculectomy

Francis et al.: Selective Laser Trabeculoplaty after Failed Trabeculectomy in Open Angle Glaucoma (31): 20 patients

Table 8: Results from Francis et al.		**p-Value**
Mean pre laser IOP (mmHg)	20,8	
Mean IOP after 12 months (mmHg)	16,3	
Reduction of the mean IOP in the first 12 months (mmHg)	4,5 (19,5%)	**< 0,001**

After failed trabeculectomy, IOP was reduced by SLT significantly.

Töteberg-Harms et al.: Selective laser trabeculoplasty following failed combined phacoemulsification cataract extraction and ab interno trabeculectomy. (32): 13 patients
"Median time to failure after SLT was 3,6 +- 0,8 months."

Cyclophotocoagulation

Lin et al.: Contact Transscleral Neodymium: Yttrium–Aluminum–Garnet Laser Cyclophotocoagulation: Long-term Outcome (33): x patients

Table 9: Results from Lin et al.	IOP	p-Value (compared with pre-treatment values)
Pre-treatment IOP (mean +- SD, mmHg) 68 patients	36,6 +- 10,1	
IOP after 1 year of follow-up (mean +- SD, mmHg) 49 patients	22,6 +- 11,3	< 0,001
IOP after 5 years of follow-up (mean +- SD, mmHg) 31 patients	21,8 +- 13,3	< 0,001
IOP after 10 years of follow-up (mean +- SD, mmHg) 28 patients	18,9 +- 12,2	< 0,001

The patients undergoing cyclophotocoagulation had glaucoma refractory to conventional treatment and were receiving the maximum-tolerated medical therapy.

Chen et al.: Endoscopic photocoagulation of the ciliary body for treatment of refractory glaucomas. (34): 68 patients

Table 10: Results from Chen et al., mean follow-up of 12,9 months		p-Value
IOP reduction (mean +- SD, mmHg)	27,7 +- 10,3 to 10,0 +- 6,7	< 0,0001

In refractory glaucoma, IOP was reduced significantly by endoscopic cyclophotocoagulation.
„With the exception of eyes that underwent combined endoscopic cyclophotocoagulation and cataract extraction, all had failed maximally tolerated medical therapy, and most had a history of one or more unsuccessful glaucoma surgeries."

3.3 Discussion

3.3.1 Medical treatment

Medication for the chronic open-angle glaucoma is always applied topically, nearly never systemically. Systemic application is only recommended if treatment is aimed to drop IOP promptly, like in case of IOP spikes and the angle-closure syndrome. The medical treatment is one of the three treatment columns in antiglaucoma therapy and up to now it has also been the column used primarily if chronic open-angle glaucoma is diagnosed. Now laser treatment is also considered to be performed as first treatment, but medication hasn't become less important and can be administered additionally to all the other treatment columns. Medication is needed to boost and to prolong the success of previous surgery or laser treatment.

Some general rules need to be considered if pharmacological actives are prescribed. I couldn't find any argument why these rules should not be important or less relevant after failed trabeculectomy: (19) (20) (18)

- If the active fails that has been chosen primarily, a different one should be administered. Only if this one fails partially, it may be hypothesised that one agent is not enough to treat IOP and a second one should be given additionally. Treatment with up to three agents is tolerable and if they still do not lower IOP satisfyingly, other treatment columns need to be considered.
- If more actives are taken, they should tackle IOP via different mechanisms of action und therefore they should never be from the same group. If they operated on the same principle, they would not have an additive impact on IOP drop.
- If more eye drops need to be taken together, at least 3-5 minutes need to be passed between the single applications.
- If possible, combination products, eye drops that include all the agents in one single solvent, should be preferred to many different application systems because compliance decreases with the number of systems used.

Which active should be chosen for primary treatment? Which combinations have proved effectiveness? These questions can't be answered in general, because the effect of agents depends on the individual patient and patients react differently. However, some guidelines are still offered to keep treatment as standardised as possible. Most important to mention is that the patients' benefit depends highly on the compliance and hence, on the balanced relation between IOP drop and severeness of side effects. The contraindications, the individual situation, the handling of side effects, the compliance, the interaction between agents as well as the impact on IOP need to be considered in decision making:

For most patients, a prostaglandin derivate or a beta-blocker is chosen primarily. Prostaglandin derivates are superior in IOP drop, although local side effects, like listed in *Table 4*, are expected to occur. However, the habituation effect reduces the severity of side effects most commonly. If side effects overweigh the benefit or compliance drops, the beta-blockers should be considered. Their risk for dangerous systemic side effects is accepted in this situation but should be minimised by taking detailed medical history. Ocular side effects are very rare, the pupil width as well as the accommodation remains unaffected and IOP drop is satisfying as well. Timolol is the most frequently used beta-blocker and no other beta-blocker is believed to be more effective. The different prostaglandin derivates are comparable according to their impact on IOP and their side effects. However, if one agent fails and application needs to be stopped, a second one might be more successful. (20)

Carbonic anhydrase inhibitors (Dorzolamid, Brinzolamid) as well as the α2-agonist Brimonidin - Apraclonidin is useful in an acute setting - can be used for monotherapy as well, although they are primarily less frequently prescribed and more preferred as additional agents, mainly together with a beta-blocker. They lower IOP less strongly in comparison to other agents. The effect of Brinzolamid and Dorzolamid on IOP has been shown to be similar although their tolerability profile is slightly different. Brinzolamid leads to less stinging on installation, but to more side effects over the course of time. (20) (35)

The role of miotics in antiglaucoma treatment is decreasing due to their nasty ocular side effects, but they are still useful for the treatment of the angle-closure syndrome. They are not in use for primary administration in the treatment of the open-angle glaucoma anymore. (20)

To sum up, prostaglandin derivates are most often prescribed as primary agents, especially due to their high impact on IOP and their lack of systemic side effects. If not successful or suitable, mostly because of their nasty ocular side effects, a beta-blocker is most commonly the second choice. The main advantage of beta-blockers is their outstanding tolerability profile and the good compliance. Their risk for dangerous systemic side effects should be minimised but finally needs to be accepted. Brimonidin is less likely the second choice because compliance is lower if compared to the one of beta-blockers, it goes down due to

tiredness and low blood pressure. While the side effects of beta-blockers are rare but dangerous, the ones of Brimonidin are more present. If a prostaglandin derivate has already been dropped because of bad compliance, a more comfortable agent is needed. The lower capacity of carbonic anhydrase inhibitors for IOP reduction might be the reason why they are less likely prescribed as second choice.
Of course, this ranking should not be understood as the common approach in medical antiglaucoma treatment, it should just give an idea of the common steps and how decision might be made in clinical practice. The individual conditions, contraindications and demands of the patients could change the ranking completely.
All the presented agents are also in use after failed trabeculectomy. Patients in this disease stage have mostly gained long clinical history. They will have already been treated with many different agents, mostly with a triple combination of antiglaucoma agents and will have gained experience on tolerability. If still necessary, these patients should keep the agents that they have tolerated in the past. If new agents need to be administered, the same rules, as discussed above, should guide the treating ophthalmologist.
Situation changes for pregnancy. The antiglaucoma drugs have been classified by the "United States Food and Drug Administration" (36). None of the available drugs is proven to be safe for the foetus. Subsequently it's recommended to avoid medication as far as possible. Laser treatment is of advantage although studies have shown evidence that it is less effective in young adults. Surgery is controversially discussed due the possible demand for postoperative medication and the increased risk of anaesthesia. The contraindication of antimetabolites limits success as well.

3.3.2 Laser treatment

Trabeculoplasty and of cyclophotocoagulation need to be discussed separately because they play different roles in the treatment of the open-angle glaucoma.

3.3.2.1 Trabeculoplasty

This chapter follows the one on medical treatment. Till years ago, medication was the primary therapy option and laser treatment would have only been considered if medical treatment had failed. However, guidelines should never be understood as a steady set of rules indicating the one and only way to treat patients, they are formed in an attempt to summarise the published data on a specific topic and always need to be adapted to the current standard of knowledge. Due to new data, indications for laser treatment, in particular for laser trabeculoplasty, are expanded beyond the current scopes of administration. Several studies have been carried out to compare medicine to laser treatment as primary treatment option. One of the main ones was the "Glaucoma Laser Trial (GLT)" (37) reporting superiority of ALT over medical treatment. The study design was criticised and some aspects need to be questioned, but the main message seems to be true: The intention was to show non-inferiority of laser treatment as primary therapy option, if compared to medication only, and the reported non-inferiority could have been confirmed in many other studies. Subsequently ophthalmologists concluded that "The option of LTP [laser trabeculoplasty] as first-line treatment for patients with newly diagnosed OAG is advantageous in terms of efficacy, adherence, and costs." (38) Compared to prostaglandin derivates, which are the most powerful IOP lowering drugs and reduce IOP by 20-35% maximally, laser trabeculoplasty is believed to reduce IOP by 10-40% in the first 6 months. (5) Its IOP lowering potential is high, although the statistical scatter is high as well. IOP reduction is highly influenced by pre-laser IOP. In eyes with an IOP of 30mmHg or above IOP reduction should be between 39-50%, while the reduction should only be between 3-4% in eyes with an IOP of 20mmHg or lower. (22)

However, which patients do benefit the most from primary laser trabeculoplasty? For sure, patients with a poor compliance because trabeculoplasty is carried out once and the effect lasts for months to years. Also patients which do not tolerate eye drops might be great candidates for initial trabeculoplasty. However, on the basis of the given data, also patients who do not want to take eye drops regularly, maybe in order to maintain a high quality of living, could be advised to undergo trabeculoplasty. Laser trabeculoplasty is contraindicated for inflammatory glaucoma and angle-closure glaucoma and also if visibility conditions are bad for the ophthalmologist, if IOP control needs to be achieved fast and if complications have been documented in the other eye. (22)

Before I am going to discuss the role of laser trabeculoplasty after failed trabeculectomy, the differences between both types of trabeculoplasty, SLT und ALT, need to be discussed in order to make decision for one of both methods easier. First of all, the IOP lowering effect should be compared, then the complication rates should be focused:

"In terms of IOP lowering effect, there is no difference between SLT and ALT.", is the conclusion of a current review, written by McAlinden in 2014. (29) I could not find one ophthalmologist who disagrees with this point of view. It seems to be well accepted. In subchapter 3.2.1.1, the results of Bovell's study, comparing the effect of SLT to the one of ALT over a follow-up of 5 years, are provided representatively for all other studies due to its long follow-up. If *Table 5* is studied closely, someone easily realises that total energy and total energy per µm is by far less for SLT than for ALT and diode laser. SLT uses less energy and is still that effective like ALT. Hence lower energy does not implicitly mean lower IOP reduction. However, there is a second interesting observation: While the spot size of argon laser is approximately 50µm and while the spot size of diode laser is about 100µm, the spot size of SLT is multiply bigger. By SLT, the biggest area is tackled. The IOP reduction of the different laser types seems to be comparable because the lower energy seems to be compensated by the bigger area.

However, these results cannot be transferred to the complication profile. The complication rates of SLT and ALT are not comparable. The spectrum of complications is the same, but they appear to be more severe after ALT than after SLT. (39) Someone might conclude that energy is a risk factor for complications while it does not seem to influence IOP reduction. The severity of complications becomes less with the decrease in the energy transmitted per µm. However, does this observation really make sense? Yes. Complications often result from the destruction or affectation of relevant anatomical structures. If the energy that is transmitted per µm is reduced, the extent of affectation is presumed to be less, although IOP reduction remains the same due to the increased affected area. In contrast to IOP reduction, the incidence of complications is more associated with the damage of a specific structure. It's known that SLT selectively targets melanin pigment in the trabecular meshwork and leaves non-pigmented structures unaffected, while ALT causes mechanical opening of the trabecular spaces too. (5) The trabecular meshwork is thermally damaged by ALT and as a consequence damage increases with further ALTs. Hence the repetition of ALT is not recommended. (5)

The anterior chamber reaction is an exception from the rule. Its incidence is higher after SLT than after ALT. (40) It seems to be a complication, whose appearance mainly depends on the size of the treated area and does not seem to be linked directly to a specific structure.

Last but not least, I need to mention the micropulse laser trabeculoplasty MLT. It is quite a new but promising form of laser trabeculoplasty with few safety concerns and good IOP reduction, being about 20%. (41) Hence it can be performed alternatively to SLT. It is even discussed whether it is more successful than SLT, especially for patients with a high risk of post-laser IOP spikes. However, large multicentre trials are still missing. (42)

With the given information, the role of trabeculoplasty should finally be discussed after failed trabeculectomy. In general, trabeculoplasty has already been performed prior to surgery and therefore recommendation of repeated trabeculoplasty seems to be a condition to consider trabeculoplasty after failed trabeculectomy. If repetition of trabeculoplasty were not recommended in general, the role of trabeculoplasty after failed trabeculecotmy would not need to be discussed at all.

Retreatment is defined as trabeculoplasty after a complete 360°-treatment. (22) Retreatment is possible for SLT, but only in exceptional cases for ALT due to the accumulative side effects. (5) However, is it also effective? Data is not very consistent and rare. For sure, re-treatment has a certain impact on IOP, the question is only raised on its extent. In a retrospective analysis, Hong et al. reported a lower decrease in IOP for the second than for the first SLT, but the differences were, apart from the first to the third month, not statistically significant. They concluded that "repeat 360° SLT may be safe and effective after an initially successful 360° SLT has failed." (30) SLT does not seem to suffer from a prior ALT either, while repeated ALT does. (40) Proven is that IOP reduction decreases with each further ALT. (43)

The provided data clearly demonstrate superiority of SLT in comparison to ALT and SLT is proven to be the better option.

Medication is not believed to have an impact on the outcome of laser trabeculoplasty. However, ALT is believed to alter the outcome of trabeculectomy. SLT should not have any influence. (22) (5) This assumption again favours SLT from the very beginning.

Success of re-treatment with SLT is proven and subsequently the condition for trabeculoplasty after failed trabeculectomy is fulfilled. Francis et al. (31) have finally measured the impact of SLT after failed trabeculectomy. "This study demonstrates mild to moderate success of SLT in lowering IOP in the short- and intermediate-term in persons with open angle glaucoma after previously failed trabeculectomy."(31), is written in the discussion. Success has been documented, although it has been shown to be modest. The study has been carried out on patients, who are reluctant or unwilling to undergo further surgery.

In a different trial, investigating the effect of SLT after failed combined phacoemulsification cataract extraction and ab interno trabeculectomy, the results of re-SLT are not promising. (32) The SLTs were reported to be initially successful but were reported to fail after 3,6 +-

0,8 months. Time to failure was very short and SLT could only prolong success of primary trabeculectomy for some months. Subsequently a further surgical procedure could have been only delayed by some months, what's not a strong argument to justify an additional intervention, even if this additional intervention is characterised by a low complication profile.

3.3.2.2 Cyclophotocoagulation

In chapter 3.2.1.2, the results of two studies are listed exemplarily to show the effectiveness of cyclophotocoagulation in the treatment of refractory glaucoma. (33) (34) IOP reduction seems to be high if compared to trabeculoplasty and medication. Both studies have been carried on with patients suffering from glaucoma being refractory to conventional treatment. In the second study, the one by Chen et al., most patients even had a history of one or more unsuccessful glaucoma surgeries. However, success was also limited. After 10 years of follow-up, 51,5% of the eyes treated with contact transscleral Nd:YAG laser have failed, most of them (40%) during the first year of follow-up. (33) Chen's (34) results only described the development over a follow-up of 2 years, but the trend was similar. Nevertheless, cyclophotocoagulation seems to be a useful procedure. However, which are the indications and which form is the better one?

TCP can be performed by Nd:YAG- and diode laser. Both reduce IOP equally, without any statistically relevant difference. (44) Youn et al. only emphasise the technical advantages of diode laser, which are a smaller size, a more convenient portability and a longer durability. Hence they believe that diode laser is the better option.

Superiority could not have been proven, either for TCP nor for ECP. The complication profiles are similar. If cyclophotocoagulation is performed together with cataract surgery, the endoscopic method will be preferred. In this case, all the additional side effects of ECP listed in chapter 3.1.2.2 do not have an impact on the final outcome because they are also side effects of phacoemulsification and therefore have no additional impact. They only need to be considered if ECP is performed as single intervention, but then TCP should be favoured. The risk of conjunctival surface burns, a potential side effect of TCP, is generally more likely accepted than the additional risks raising from the invasiveness of ECP. (25) (27)

ECP is discussed to be of advantage for patients with atypical ciliary body morphology, like children, because it provides a direct view to the ciliary body. Hence the target points can be detected more precisely. The treatment of a 3,5 –year old boy with ECP was reported to be successful over a period of 6 months, although it had followed the failures of 3 TCPs. (45) Hence, ECP has the potential to lower IOP more successfully than TCP.

Is cyclophotocoagulation also recommended after failed trabeculectomy? Although the answer is only based on level III evidence, meaning that evidence is obtained from non-randomised observational studies, case-control studies, cohort studies and cross-sectional studies (46), the answer is clear and ophthalmologists have reached agreement: "Cyclophotocoagulation is indicated for patients with refractory glaucoma who have failed trabeculectomy or tube shunt procedures […]. It may be useful for patients whose general health status precludes invasive surgery or who refuse more aggressive surgery (i.e., filter or tube). It is also useful in emergent situations, such as the acute onset of neovascular glaucoma." (27) In 2008, Lin writes: "Both contact and noncontact TCP have been shown to be effective surgeries for treating refractory glaucoma in which medications and/or other surgeries have failed." (47) And last but not least, the study by Chen et al. (34) on endoscopic cyclophotocoagulation, cited in chapter 3.2.1.2, was also carried out on patients that had failed on maximally tolerated medical therapy and most of them had a history of one or more unsuccessful glaucoma surgeries.

Cyclophotocoagulation is not only successful after failed trabeculectomy, it should even increase the outcome of trabeculectomy. In a brand-new retrospective analysis, published in June 2016, 12 eyes which had undergone diode laser cyclophotocoagulation prior to trabeculectomy were assessed. (48) The reason might be that complications of trabeculectomy are known to increase with preoperative IOP. Hence, the combination of trabeculectomy and cyclophotocoagulation could be useful to reach long-lasting IOP control.

The final and most important question is whether cyclophotocoagulation should be performed as a single procedure and should be preferred to second trabeculectomy if the primary has once failed. The mentioned analysis by Singh et al. (48) suggests that a combination of both procedures might be useful, but definite evidence is missing. As this question compares laser treatment, a non-surgical option, to surgical treatment, it should be taken up in the end of the chapter on the surgical therapy options.

4 INDICATION FOR FURTHER SURGERY

4.1 Surgical treatment options

The surgical treatment options are divided in penetrating and non-penetrating procedures:

4.1.1 Penetrating surgery

In penetrating surgery, aqueous outflow is enhanced by creating an artificial transmural filtration pathway. The anterior chamber is entered.

Filtration surgery: It refers to the creation of a pathway next to the trabeculum. It either refers to trabeculectomy as well as to tube shunt surgery or to trabeculectomy only. In literature, this term isn't used consistently and therefore it's avoided in this essay.

4.1.1.1 (Second) Trabeculectomy

"Trabeculectomy is glaucoma filtration surgery that lowers IOP by creating a fistula, protected by a superficial scleral flap, to allow aqueous outflow from the anterior chamber to the sub-Tenon space." (5)

Steps: The main steps of this procedure should be explained shortly as the exact strategy may differ from surgeon to surgeon: (5)

- Preparation of a superior limbus- or fornix-based flap of conjunctiva and Tenon's capsule.

- Preparation of a superficial limbus-based, rectangular (mostly 4x5mm) scleral lap, formed out of the superficial layer of the sclera.
- Excision of a limbus-based block of deep sclera, that includes trabecular meshwork and parts of the cornea.
- Creation of peripheral iridectomy in order to prevent blockage of the internal opening.
- The superficial scleral flap is sutured at its posterior corners.
- The conjunctiva/Tenon's capsule is sutured. A bleb begins to form.

Antimetabolites should be used to inhibit the physiological wound healing as well as to keep IOP reduction more constant throughout the years. Nowadays, application is very common but though it administration needs to be done with caution because it increases the probability for postoperative hypotony. A trabeculectomy with the application of an antimetabolite is described by the term "augmented trabeculectomy". The effect of antimetabolites depends on their concentration and the time they are administered. The parameters need to be adjusted for the individual patients.

The following two substances are in use: (5)

- 5-Fluorouracil 5-FU
- Mitomycin C MMC

Antimetabolites are also administered postoperatively if bleb failure occurs, after augmented as well as after non-augmented trabeculectomy. More information about the use of antimetabolites for bleb failure is provided in chapter 2.

<u>Indication:</u> Primary trabeculectomy is indicated if target IOP isn't reached

- on maximally tolerated medical treatment and
- after laser trabeculoplasty.(2)

In cases of noncompliance, advanced visual-field defect and rapidly progressive visual-field loss trabeculectomy might be indicated earlier. After failed primary trabeculectomy, trabeculectomy might be indicated again. Conditions and alternative procedures are discussed later. (2)

Khaw et al. declare trabeculectomy to be the "'gold standard' GFS (glaucoma filtration surgery) for many types of glaucoma"(2) in their review printed in the 3rd edition of "Albert & Jakobiec's Principles and Practice of Ophtalmology". However, this does not mean that trabeculectomy is superior to other surgical methods by itself, it just means - in consideration of the surgeon's skills and other influencing factors - that trabeculectomy is the most frequently performed surgery. The term "gold standard" is commonly used but often misinterpreted and therefore I feel obliged to state its true meaning shortly. It was primarily used in the economic context, describing the exchange ratio between gold and the currency of interest. Transferred into medicine, the gold standard is defined as the best treating, diagnostic or scientific method for an individual patient (49), but not the best option for all patients. Subsequently, factors like the surgeon's skills or the availability of different specialists influence decision making. The best method for the individual patient is the one from which the surgeon as well as the patient expect the best individually defined success.

Complications: The aim of trabeculectomy is an adequate IOP reduction. The operation might be ineffective in case of filtration failure, when IOP reduction is too small, but might also result in overfiltration, called persistent hypotony. Complications often lead to one of these two final stages. In order to make the comparison between trabeculectomy and tube shunt surgery easier, the complications of trabeculectomy are presented in the following chapter next to the possible complications of tube shunt surgery.

To evaluate blebs consistently, the Moorfield's Eye Hospital (London) has developed a bleb grading system. Blebs should be described in the following three categories: Their expansion, their height and their vascularity. Reference photographs are provided on the website. (50)

4.1.1.2 Tube shunt surgery

The idea behind tube shunt surgery is simple. Surgeons intend to create a bigger bleb than in case of trabeculectomy and transfer it to the equatorial region by the implantation of a tube shunt. The created pathway through the sclera is kept open by the implant - scleral cell proliferation is no risk factor for inadequate IOP reduction anymore - but the tube might get blocked and the scarring of conjunctival and Tenon's capsule tissue is still of importance. Tube shunts consist of a silicone tube, which is inserted into the anterior chamber, and a plate, that is fixed on the episclera and is thereby placed in the sub-Tenon's space. The first tube shunts, the Molteno implants, were modified in 1969, just one year after trabeculectomy had been introduced. Until now, they have underwent further development, are still very popular and remain one of the three common groups for classic tube shunt devices used in clinical practice. (1)

The principle is the same for all tube shunts. The engine of filtration is, like in case of trabeculectomy, a passive, pressure-dependent flow. The higher the IOP levels are, the more aqueous is shunted. IOP is the driving force behind filtration and needs to outweigh the pressure created by the surrounding Tenon's capsule. Aqueous that has passed the plate, pools in the sub-Tenon's space and a tissue capsule is formed around the implant. Capsule thickness as well as capsule surface area majorly influence final IOP. (51) (5)

Tube shunts are divided into two groups, those with pressure sensitive valves, which are intended to regulate outflow upon minimal IOP, and the non-valved ones. (5)

- Molteno: Silicone tube connected to one or two polypropylene plates (13mm in diameter).
- Baerveldt: Silicone tube connected to a silicone plate of large area.
- Ahmed: Silicone tube shunt connected to a silicone sheet valve held in a polypropylene body.

The following table provides the sizes for the different types of tube shunts:(51) How decision for a certain size is made should be discussed in chapter 4.3.1.2.

Table 11: Tube shunts - Sizes in mm2

Ahmed glaucoma valve implant	Baerveldt glaucoma implant	Molteno implant
96 (S3) 184 (S2) 364 (B1) 96 (FP8) 184 (FP7) 364 (FX1)	250 350 500	74 (pediatric) 134 (single-plate) 268 (double-plate)

<u>Steps:</u> The main steps of this surgical procedure should be explained shortly, as the exact technique depends on the type of tube shunt used: (51)

- Preparation of a limbus- or fornix-based flap of conjunctiva and Tenon's capsule, for example in the superotemporal quadrant of the bulbus, because in this quadrant postoperative strabism is less frequent.
- Dissection of conjunctiva and Tenon's capsule from sclera to create space for the plate.
- The plate is positioned between the rectus muscles, about 10mm posterior to the limbus.
- A tight entry is created with a needle into the anterior chamber and the tube is inserted for 2-3mm. It can also be inserted through the pars plana when pars plana vitrectomy has already been performed.

- Tube coverage with a 4x4mm big patchgraft, that consists of donor sclera, cornea, pericardium, etc.
- Conjunctiva is sutured and radial relaxing incisions are set.

Indication: Tube shunt surgery might be indicated after failed trabeculectomy or after failed tube shunt surgery. Tube shunt surgery is seldomly performed as primary procedure. The circumstances under which tube shunt surgery is the most promising technique are incompletely defined and indication needs to be discussed individually.

Complications: In the following I am going to focus on possible complications in general, especially in contrast to trabeculectomy. The different types of tube shunts regarding their efficiency and safety profile should be compared in chapter 4.3.1.2.
For tube shunt surgery, as well as for trabeculectomy, complications should be divided into intraoperative, early and late postoperative ones.
Complications might have a negative impact on IOP reduction, what means that the effect of the procedure decreases and glaucoma continues to progress, or might cause hypotony, what leads to decompression retinopathy and choroidal effusion, two pathologies that are clinically hard to distinguish due to their overlapping pathogenic mechanism und their similar clinical appearance:

- Decompression retinopathy is the clinical manifestation of retinal haemorrhages, sometimes with oedema of the optic nerve. Also choroidal detachment might be detected. The exact pathogenesis remains unclear. It’s assumed that the retina moves forward due to the abrupt decrease in IOP. Subsequently the shift is deemed to compress the central vein causing the retinal pathologies listed above. (52)
- Choroidal effusion is the accumulation of fluid in the suprachoroidal space, commonly in hypotonous eyes. Proteins diffuse from leaking capillaries into the tissue and cause oedema, but also bleeding causes choroidal effusion. (53)

Hypotony as well as increased IOP might occur intraoperatively, early (often defined as complications in the first three months) and late postoperatively.
In the following, I am going to list the complications, in dependence on their influence on IOP. After each block, explanation and treatment options follow:

Table 12: Reason for hypotony. Overdrainage might be caused by ... (2) (51) (54)	
▪ Wound leak	
Only in case of tube shunt surgery	**Only in case of trabeculectomy**
▪ Tube erosion	

- Wound leak is a possible complication of both procedures and is synonymously called bleb leak. After tube shunt surgery it may occur due to hypotrophy, caused by the interaction between the implanted tube shunt and the tissue around. In case of occurrence, the tube shunts need almost always to be removed. In case of early wound leak, it is directly related to the operation. Either the wound hasn't already healed and therefore aqueous gets lost or technical performance hasn't been desirable. Late wound leak is caused by necrosis of the conjunctiva that overlies the trabeculectomy. All in all wound leak typically follows operations, in which antimetabolites, especially MMC, have been used.

Treatment of hypotony: Severe cases require further surgery. Injection of a high-density viscoelastic or autologous blood might be successful in case of bleb leak. If not, tighter sutures need to be set or the bleb needs to be removed and replaced by amniotic membrane, by a conjunctival patch autograft or by a scleral graft. Steroids or antibiotics might be helpful if hypotony is triggered by infection or inflammation.

Table 13: Ineffective IOP reduction is caused by occlusion of the filtering pathway and by elevated pressure in the sub-Tenon's space. Specific reasons are (2) (51) (54)	
▪ Fibrosis ▪ Hyphema ▪ Inflammation ▪ Vitreous prolapse ▪ Aqueous misdirection (malignant glaucoma)	
Only in case of tube shunt surgery	**Only in case of trabeculectomy**
▪ Malposition and migration of the tube shunt	▪ Pupillary block

- Fibrosis due to the proliferation of fibroblasts, especially in the conjunctiva and the Tenon's capsule.

  Treatment: Injection of antimetabolites.
- Hyphema especially occurs during tube shunt surgery for neovascular glaucoma. It happens intraoperatively, when blood vessels are injured.

Treatment: If observed, the surgeon should try to irrigate the blood out through paracentesis.

- Inflammation: Superficial infections might progress and lead to endophthalmitis. High-risk patients need to be identified preoperatively. As the application of metabolites increases the incidence of late infection, their administration needs to be adjusted to the patient. Removing sutures and minimising lashes might be attempts to reduce early infection. Haemophilus and Streptococcus are the most common organisms causing bleb related endophthalmitis.
  Treatment: Topical or systemic antibiotics. A vitrectomy should be considered. In severe cases, the tube shunt needs to be removed.
- Vitreous prolapse might block the tube shunt or the trabeculectomy.
  Treatment: Anterior vitrectomy is indicated.
- Aqueous misdirection (malignant glaucoma): Ciliary processes are assumed to rotate anteriorly and subsequently assumed to press against the lens, causing a ciliolenticular block. The so called first reluctance (between the lens and the iris) of the physiological aqueous outflow pathway is increased. As a consequence, the iris is pressed anteriorly, presenting in a shallow anterior chamber and high IOP.
  Prevention: Overdrainage should be avoided and high risk patient should get topical atropine after operation. The reduced axial length of the bulb is a risk factor.
  Treatment: Application of mydriatics and cycloplegic agents. Nd:YAG laser treatment is, if iridotomy has not been performed, indicated to create communication between the anterior and the posterior chamber via a hole in the iris.
- Pupillary block might occur after non-patent peripheral iridectomy.
  Treatment is iridectomy or Nd:YAG iridotomy.
- Malposition and migration of the tube: Movement of the tube.
  If IOP reduction becomes ineffective or the tube touches the cornea, surgery is indicated.

Table 14: Complications with no effect on IOP (2) (51) (54)	
▪ Corneal decompensation ▪ Cataract formation ▪ Diplopia	
Only in case of tube shunt surgery	**Only in case of trabeculectomy**
▪ Scleral perforation	

- The reasons for corneal decompensation aren't completely solved. Microtraumas, but also biological processes, are considered. The incidence is higher in patients with preoperative endothelial damage and patients with penetrating keratoplasty. Corneal oedema follows.
  Treatment: Penetrating keratoplasty or descemet membrane endothelial keratoplasty (DMEK). In case of hypotony related decompensation, IOP increasing measures are indicated.
- Cataract formation: Lens-corneal touch, lens trauma, inflammation, hypotony and the application of intraoperative MMC trigger formation.
  Prevention: Preventive treatment of the listed risk factors. Surgery for treatment.
- Diplopia: Either the bleb or the tube interferes with muscles and motility causes scarring and motility disturbances. The worst form is persistent strabism. Diplopia might disappear if periocular swelling resolves.
  Treatment: Application of prism spectacles. Strabismus surgery should be considered if diplopia appears to be constant.
- Scleral perforation might result in retinal detachment or endophthalmitis.
  Treatment: Surgery.

Data for incidence of single complications does vary from publication to publication strongly. The TVT provides favourable comparison of the complication rates of trabeculectomy and tube shunt surgery. The overall complication rate appears to be lower in the tube shunt group. Results are provided in chapter 4.2.1 and discussed in detail in chapter 4.3.1.1.

Mini-tube shunts

The ongoing research work on tube shunt surgery led to the development of mini-shunts. Several types of different producers are in use: The Ex-Press™ Mini-Shunt and the iStent®. (5)

- The ExPress® Mini-Shunt is a valveless titanium MR-compatible stent. It drains aqueous into the subconjunctival space and in trabeculectomy it is placed between the scleral flap and the bed. (55)

- The iStent® is a tiny titanium micro-bypass stent and is implanted in the trabecular meshwork and drains into the Schlemm's canal. According to the producer, it is the smallest medical implant known. (56)
- The XEN® Gel Stent is a small tube made out of gelatin and is injected via a needle, that is inserted via the anterior chamber into the subconjunctival space. (57)
- The CyPass® Micro-Stent is a small tube that is inserted between the sclera and the ciliary body. It increases the aqueous drainage via the uvea. (58)

4.1.2 Non-penetrating surgery

In contrast to penetrating surgery, which is characterised by an artificial filtration pathway that allows communication between the anterior chamber and the sub-Tenon's space, the anterior chamber is not entered for non-penetrating surgery. The resistance of the natural filtration pathway is reduced by manipulating the Schlemm's canal as well as the trabecular meshwork. (59)

According to the definition of non-penetrating surgery, the surgical success is less determined by the tension of the closed flap, it is more influenced by the manipulation of the IOP regulating anatomic structures.

The mechanism of the filtration process after non-penetrating surgery hasn't been solved in detail yet and studies are carried out to investigate the altered pathway in glaucomatous eyes. However, four ways of aqueous drainage are discussed in literature: (59)

- Subconjunctival filtering bleb
- Intrascleral filtering bleb
- Suprachoroidal filtration
- Episcleral vein outflow via Schlemm's canal

The understanding of the exact mechanism might enable surgeons to improve the existing surgical techniques. A good example is non-penetrating surgery itself. The assumption that the Schlemm's canal and the anatomical structures situated behind influence IOP encouraged surgeons to develop these presently well-known techniques. The involvement in the IOP-regulating system has finally been proven by the success of this kind of surgery.

The range of possible complications is similar to the one of penetrating surgery:

- Complications resulting in hypotony/overdrainage
  - Wound leak also occurs after non-penetrating surgery. As the trabeculo-Descemet's membrane remains intact after regularly performed surgery, hypotony is mostly limited. Moreover, postoperative wound leak should even indicate effectiveness of filtration in the future. According to Mendrinos' et al. review printed in "Albert & Jakobiec's Principles and Practice of Ophthalmology", not one single case of flat anterior chamber has been reported after non-penetrating surgery. Nevertheless, if it exists, it needs to be enormously seldom. The incidence of choroidal detachment is also very low. Detailed data are provided in chapter 4.2.3.

    Treatment: Topical steroids over some weeks should increase IOP. (60)

    The perforation of the trabeculo-Descemet's membrane is a special case of wound leak that mostly occurs during operation if incision has been made too deeply and occurs seldom as postoperative complication. The severest consequences are a flat anterior chamber and iris prolapse as well as synechia formation. Treatment depends on the type of perforation:(59)
    - Transverse tears: Perforation occurs at the junction of the anterior trabecular and the Descemet's membrane. Iris prolapse is the consequence and surgery is required. Installation of viscoelastic material and the positioning of an implant are possible therapy options. (59)
    - Trabeculo-Descemet's membrane holes: With regard to treatment, the holes need to be categorised by size. Small ones, which do not affect physiological anatomy should be ignored, while large ones, defined by the occurrence of complications like flat anterior chamber or iris prolapse, require further treatment. If the depth of the anterior chamber is affected only, viscoelastic material should be injected to stabilise anatomic structures, especially the iris. After iris prolapse, trabeculectomy needs to be performed. (59)

      However, Sarodia et al. argue that trabeculectomy is, if performed after penetration, at disadvantage compared to planned trabeculectomy due to unfavourable flap design. (61) Contrarily, Sanchez (62) reports comparable results and subsequently encourages surgeons to learn non-penetrating surgery.

- Complications leading to ineffective IOP reduction: Apart from pupillary block and malposition of the tube, all complications listed in 4.1.1.2 are of importance. The pathophysiological mechanisms remain the same, just the incidence of each complication differs.
  In contrast to penetrating surgery, the complications do not include pupillary block. It only occurs after non-patent peripheral iridectomy during filtration surgery. As the anterior chamber is not entered for non-penetrating surgery, risk is minimally low. Malposition and migration of an implant might only happen if any sort of implant is used.
- Complications with no effect on IOP: Comparable with the complications listed in 4.1.1.2.
- Descemet's membrane detachment (59)

Apart from some exceptions, the complication profile remains the same for non-penetrating surgery. An overview of incidences is provided in chapter 4.2.3 (Results).

The most common types of non-penetrating surgery are the deep sclerectomy, the viscocanalostomy and the trabectome. These methods are presented in detail in the following subchapters.

4.1.2.1 Deep sclerectomy

The conjunctiva is incised and a scleral flap making up one third of scleral thickness is created. It should measure 5x5mm and should have its fold at the inner line of the square, located in the clear cornea 1-1,5mm next to the limbus. A further square is cut out of the sclera, measuring 4x4mm, and should adjoin to the inner line of the primary square. The anterior chamber mustn't be entered, the so-called trabeculo-Descemet's membrane, consisting of peripheral Descemet's membrane and the anterior trabecular meshwork, should remain intact as it functions as the natural outflow resistance. This part of the surgery is the most challenging one because the remaining layer is quite thin. In the following step, the so-called ab externo trabeculectomy, the juxtacanalicular trabeculum is removed and the Schlemm's canal, which is detected by the parallel disposal of the fibres of the trabeculo-Descemet's membrane, is opened. Finally the scleral flap is sutured at the two corners. An implant is placed under the scleral flap to prevent the flap from collapsing. The conjunctiva and the Tenon's capsule are sutured too. (60)

4.1.2.2 Viscocanalostomy

Viscocanalostomy focuses on the Schlemm's canal as the physiologically most important filtration pathway. In order to increase its aqueous outflow, the resistance of the canal itself needs to be low while pressure difference between the juxtacanalicular region of the trabecular meshwork and the episcleral veins should be high. The first condition is realised by dilating the Schlemm's canal. High viscosity hyaluronic acid is injected into the canal. Pressure is increased by suturing the scleral flap tightly so that aqueous flow to the sub-Tenon's space is suppressed and no filtering bleb develops. In contrast to deep sclerectomy, this method is not bleb-forming. (60)

The initial steps of viscocanalostomy are the same as of deep sclerectomy. Two flaps are designed, a superficial one, which is sutured in the end and should close the operation field, and a deep one, which gets totally dissected. After revealing the trabeculo-Descemet's membrane, the Schlemm's canal is opened and the injection is performed. (60)

Canaloplasty is a special type of viscocanalostomy. The whole Schlemm's canal is cannulated with a microcatheter and a Prolene suture is implanted 360° to stretch the inner wall of the Schlemm's canal. (5)

4.1.2.3 Trabectome surgery

The anterior chamber is entered with the trabectome via a corneal incision. The surgeon approaches the iridocorneal angle from the inside and removes the inner wall of Schlemm's canal as well as the trabecular meshwork in front over a segment of 60-180°. (63)

4.1.2.4 Nd:YAG Goniopuncture

Nd:YAG goniopuncture is an adjunctive to non-penetrating surgery and aims to convert non-penetrating surgery into a micro-perforating one. The laser creates microscopic holes into the trabeculo-Descemet's membrane via shots through the anterior chamber to increase aqueous drainage through the membrane. If filtration has failed, Nd:YAG goniopuncture is performed after deep sclerectomy or viscocanalostomy respectively canaloplasty. (60)

4.2 Results

This chapter provides the most considerable data for the ongoing discussion. Without any claim to completeness, I intend to point out relevant results.

4.2.1 The tube versus trabeculectomy study

The Tube versus Trabeculectomy Study (TVT) (64) is the most relevant paper that assesses tube shunt surgery and trabeculectomy after failed trabeculectomy and/or after cataract surgery. (20% of the patients in the trabeculectomy group and 22% in the tube group were phakic.) It is a clinical trial that was conducted at 16 clinical centres in the US as well as at the Moorfields Eye Hospital “showing a persistent treatment benefit of tube shunt surgery over trabeculectomy through five years of follow-up”(64). Due to its importance the study design should be presented shortly:

Study design, methods (3): The TVT was a randomised clinical trial. Randomisation was stratified by clinical centre and type of previous intraocular surgery.

Overall, 212 eyes of 212 patients were enrolled. The patients were 18 to 85 years old and “had previous trabeculectomy and/or cataract extraction with intraocular lens implantation and uncontrolled glaucoma with IOP ≥ 18mmHg and ≤ 40mmHg on maximum tolerated medical therapy”(3). Being randomised to one of the surgical procedures, patients underwent trabeculectomy with MMC or tube shunt surgery. In the second case, a 350mm^2 Baerveldt tube was implanted.

After the procedure, patients were examined for different endpoints. IOP reduction and the rate of complications were defined as primary outcome measures.(64)

Defined by post-surgery IOP, the failure rate was determined to be a secondary outcome measure: (64)

- IOP > 21mmHg or not reduced by 20% below baseline on two consecutive follow-up visits after 3 months.
- IOP ≤ 5mmHg on two consecutive follow-up visits after 3 months.
- Additional glaucoma surgery.
- Loss of light perception.

The results of the TVT after 5 years of follow-up are provided in *Table 15*.

Table 15: Results TVT, 5 year follow-up (64) (65)		Tube group	Trabeculectomy group	p-Value
IOP (mean +- SD, mmHg)	baseline	25,1 +- 5,3	25,6 +- 5,3	0,56
	end of follow-up	14.4 +- 6.9	12.6 +- 5.9	0.12
Glaucoma medications (mean +- SD, n)	baseline	3,2 +- 1,1	3,0 +- 1,2	0,17
	end of follow-up	1.4 +- 1.3	1.2 +- 1.5	0.23
Cumulative probability of failure. Reasons for treatment failure …		29.8%	46.9%	**0.002**
- Inadequate IOP reduction		54%	40%	0.43*
- Reoperation for glaucoma		29%	26%	
- Persistent hypotony		13%	31%	
- Loss of light perception		4%	2%	
Patients with reoperations for glaucoma		8 (9%)	18 (29%)	**0.025**
Patients with reoperations for complications		20 (22%)	15 (18%)	0.29

*p = 0,43 for the difference in distribution of reasons for failure between treatment groups.

Complications in the TVT:

- Early postoperative complications: Wound leak (p = 0.004) was the only early postoperative complication that occurred with a significantly different incidence in both groups, being more frequent in the trabeculectomy group. Statistically relevant significance was also reached by the overall complication rate.
- Late postoperative complications show similar results. Bleb leak and dysesthesia, both more common in the trabeculectomy group, were the only complications with a significant difference in their incidence. Persistent corneal edema was the most frequent late postoperative complication. In contrast to early postoperative complications, the overall incidence of late postoperative complications was similar between treatment groups.(65)

To sum up, the TVT found a significantly higher cumulative probability of failure in the patients included in the trabeculectomy group after 3 and 5 years of follow-up. IOP reduction couldn't have been reported to be significantly different, although reoperation for glaucoma, what could be interpreted as severe failure in IOP lowering, was significantly higher in the trabeculectomy group.

4.2.2 Selection of the tube shunt

The studies provided in this chapter compare different types of tube shunts as primary treatment option and not after failed trabeculectomy. The need derives from the lack of studies investigating situation after failed trabeculectomy.

4.2.2.1 Ahmed versus Baerveldt

Budenz et al.: Ahmed Baerveldt Comparison Study ABC (66): 276 patients

Table 16: Results ABC, 5 year follow-up		**Ahmed group FP7**	**Baerveldt group 350**	**p-Value**
IOP (mean +- SD, mmHg)	baseline	31,2 +- 11,2	31,8 +- 12,5	0,71
	end of follow-up	14,7 +- 4,4	12,70 +- 4,5	**0,015**
Glaucoma medications (mean +- SD, n)	baseline	3,4 +- 1,1	3,5 +- 1,1	0,34
	end of follow-up	2,2 +- 1,4	1,8 +- 1,5	0,28
Cumulative probability of failure		44,7%	39,4%	0,65
Cumulative rate of serious complications		15,9%	24,7%	**0,034**
Rate of reoperation for glaucoma		20,8%	8,6%	**0,01**

The overall complication rates weren't significantly different.

Christakis et al.: Ahmed versus Baerveldt Study AVB (67): 238 patients

Table 17: Results AVB, 3 year follow-up		**Ahmed group FP7**	**Baerveldt group 350**	**p-Value**
IOP (mean +- SD, mmHg)	baseline	31,1 +- 10,5	31,7 +- 11,1	0,71
	end of follow-up	15,7 +- 4,8	14,4 +- 5,1	0,09
Glaucoma medications (mean +- SD, n)	baseline	3,1 +- 1,0	3,1 +- 1,1	0,6
	end of follow-up	1,8 +- 1,4	1,1 +- 1,3	**0,002**
Cumulative probability of failure		51%	34%	**0,013**

Similar complication rates, but hypotony related complications were only found in the Baerveldt group. This difference reached statistical significance.

Goulet et al.: (68) 192 patients

Table 18: Results from Goulet et al., 2 year follow-up		Ahmed group S2	Baerveldt group 250	p-Value
IOP (mean +- SD, mmHg)	baseline	35,3 +- 13,4	35,3 +- 12,9	0,99
	end of follow-up	19,8 +- 9,5	15,8 +- 7,9	**0,003**
Glaucoma medications (mean +- SD, n)	baseline	2,7 +- 1,2	2,8 +- 1,1	0,88
	end of follow-up	1,4 +- 1,2	0,9 +- 1,1	**0,008**
Cumulative probability of success		62%	85%	**0,03**

Complication rates are similar.

4.2.2.2 Mini-tube shunts

ExPress ® Mini-Shunt

Implantation of Express ® Mini-Shunt versus trabeculectomy (55)

Table 19: Express Mini-Shunt	Number of patients enrolled	IOP in Mini-Shunt group compared to trabeculectomy group	Complication rate in Mini-Shunt group compared to trabeculectomy group
Maris et al. (69)	100	Sign. higher, but only shortly after procedure	Sign lower
Good et al. (70)	70	No sign difference, but tendency to higher IOP	No sign difference but tendency to fewer complications
De Jong LA et al. (71)	78	Sign lower in the first 3 years	No sign difference but tendency to fewer complications
Seider et al. (72)	93	No sign difference, but tendency to lower IOP	No sign difference
Konopinska et al. (73)	85	No sign difference, but tendency to higher IOP	No sign difference but tendency to fewer complications

iStent®

Katz et al.: Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication: 119 patients (74)

Table 20: Results from Katz et al., 1,5 year follow-up	One Stent-group	Two Stent-group	Three Stent-group	p-Value
Decrease in IOP (mean +- SD, mmHg)	19,8 +- 1,3 to 15,9 +- 0,9	20,1 +- 1,6 to 14,1 +- 1,0	20,4 +- 1,8 to 12,2 +- 1,1	**< 0,001**

The IOP reduction increases with the number of iStents implanted.

I couldn't find one single paper comparing the iStent® with trabeculectomy.

4.2.3 Non-penetrating surgery

This subchapter provides the results, which are of interest for the subsequent discussion on the role of non-penetrating surgery in the surgical treatment of glaucoma, summarised and ranked by topics.

Impact of implants (used for deep sclerectomy) on IOP reduction

Many studies have been carried out to measure the impact of the implants. The studies are mainly consistent with each other. The implants should have an advantageous impact on IOP reduction, although not all of them reach statistical significance. The two biggest studies: A trial by Shaarawy (75) including 104 eyes for a follow-up period of 2 years showed a significant reduced number of medication for the implant-group while there was no significant difference reported in IOP between both groups. Sanchez (76) provides similar results. No significant difference in IOP level but significant lower rate of medication and significantly better complete success rate.

Impact of Nd:YAG goniopuncture on IOP reduction

The efficiency of Nd:YAG goniopuncture has been proven several times. The brand-new paper by Matteo (77) confirms success again. After Nd:YAG goniopuncture, IOP has been reported to be significantly lower than in the control group at each control visit ($p < 0,0001$). Follow-up has been continued over a period of 30 months. The procedure can be performed several times.

One of the largest studies, including 173 patients in need for laser goniopuncture after deep sclerectomy, was published by Anand (78) in 2010. He reports IOP control, defined by < 15mmHg, for ≥ 2 years after the single procedure. Like other authors he mentions the incarceration of the iris, as the only common complication of this treatment. Incarceration was reported in 25,4% after laser goniopuncture. Incidence was even higher in Matteo's study (77), making up 33,3%. However, he could reduce it successfully to 2,6% by pre-treating patients with iridotomy and localised iridoplasty.

Hardly any other complications were observed and in case of occurrence, they were not found to be statistically significant. (78)

4.2.3.1 Non-penetrating surgery after failed penetrating surgery

Anand, Wechsler (79): Deep sclerectomy with mitomycin C in eyes with failed glaucoma surgery (84,4% trabeculectomy, 15,6% deep sclerectomy) and pseudophakia: 82 patients

Table 21: Results from Anand, Wechsler, 3 year follow-up		p-Value
Decrease in IOP (mean +- SD)	24 +- 7,5 to 13,4 +- 4,1	**< 0,001**
Decrease in glaucoma medication (mean +- SD, n)	2 +- 1 to 0,3 +- 0,7	**< 0,05**

Deep sclerectomy has the potential to reduce IOP significantly after previous cataract- and after previous glaucoma surgery.

Mosaed, Chak (63): Results of trabectome surgery following failed glaucoma tube shunt implantation: 20 patients

Table 22: Results from Mosaed, Chak, 1 year follow-up		p-Value
Decrease in IOP (mean +- SD, mmHg)	23,7 +- 6,4 to 15,5 +- 3,2	**0,05**
Decrease in glaucoma medication (mean +- SD, n)	3,2 +- 1,5 to 2,4 +- 1,5	0,44

Trabectome surgery has the potential to reduce IOP significantly after failed tube shunt surgery.

4.2.3.2 Non-penetrating surgery versus trabeculectomy

Patients with previous eye surgery were excluded.

Table 23: Non-penetrating surgery versus trabeculectomy	Follow-up period	Non-penetrating surgery vs trabeculectomy (control group)	Decrease in IOP (mean +- SD, mmHg) during follow-up	p-Value
Sayyad et al. (80)	1 year	Deep sclerectomy	27,9 +- 5,9 to 15,6 +- 4,2	0,15
		Trabeculectomy	28,2 +- 4,7 to 14,1 +- 4,6	
Mermoud et al. (81)	2 years	Deep sclerectomy with collagen implant	26,7 +- 7,3 to 13,8 +- 3,7	≥ 0,05
		Trabeculectomy	25,4 +- 7,3 to 11,9 +- 4,4	
Chiselita (82)	1,5 years	Deep sclerectomy	27,7 +- 2,2 to 20,9 +- 4,0	**0,0015**
		Trabeculectomy	27,3 +- 2,1 to 17,3 +- 1,2	
Jonescu-Cuypers et al. (83)	0,5 year	Viscocanalostomy	31,2 +- 7,0 to 18,3 +- 5,0	**0,0202**[2]
		Trabeculectomy	28,1 +- 5,8 to 15,6 +- 3,2	

[2] Bezieht sich auf Kaplan Meier Kurve

Carassa et al. (84)	2 years	Viscocanalostomy	24,8 +- 6,7 to 16,3 +- 5,1	0,11
		Trabeculectomy	22,9 +- 7,2 to 14,0 +- 4,6	
Yalvac et al. (85)	3 years	Viscocanalostomy	36,8 +- 8,0 to 17,8 +- 4,6	0,694
		Trabeculectomy	37,7 +- 9,0 to 16,0 +- 7,1	
Gilmour et al. (86)	54 months	Viscocanalostomy	25,0 +- 4,0 to 17 +- 3,9	0,467
		Trabeculectomy	25,3 +- 4,1 to 18,4 +- 4,0	
Kobayashi et al. (87)	12 months	Viscocanalostomy	25,0 +- 2,2 to 17,1 +- 1,5	< **0,0001**
		Trabeculectomy with MMC	24,8 +- 2,6 to 12,6 +- 4,3	

In some, but not in all studies, trabeculectomy could lower IOP significantly more effective than non-penetrating surgery.

Ad *Table 24*: The incidence of the different complications is lower - often, but not always even significantly lower - for non-penetrating surgery than for trabeculectomy.

Table 24: Complications in non-penetrating surgery (Data not available)*		Inflam-mation		Hypotony related complications								Hyphema		Cataract	
				Perfor-ation		Hypotony		Flat ant chamber		Choroidal detachment					
		(%)	p-V	(%)	p-V	(%)	p-V	(%)	p-V	(%)	p-V	(%)	p-V	(%)	p-V
Anand et al. (79)	Deep sclerectomy with MMC	- *		-		6,1		-		2,4		1,2		-	
Mosaed et al. (63)	Trabectome surgery	-		0		10		-		0		-		-	
Sayyad et al. (80)	Deep sclerectomy	-		12,2		0	0,9	0	0,23	-		2,6	0,6	0	0,9
	Trabeculectomy	-				2,6		7,7		-		7,7		2,6	
Mermoud et al. (81)	Deep sclerectomy with collagen implant	0	**0,001**	11		-		0	**0,006**	5	**0,05**	2	**0,0001**	9	**0,04**
	Trabeculectomy	23				-		18		20		34		25	
Chiselita (82)	Deep sclerectomy	0	>0,05	17,6		-		0	>0,05	-		0	**0,003**	0	**0,0279**
	Trabeculectomy	12				-		18		-		41		24	
Carassa et al. (84)	Viscocanalostomy	-		24		0		-		0		12,5		-	
	Trabeculectomy	-				20		-		4		4		-	
Yalvac et al. (85)	Viscocanalostomy	-		2		4	**0,002**	-		-		4	0,307	8	**0,002**
	Trabeculectomy	-				28		-		-		8		28	
Gilmour et al. (86)	Viscocanalostomy	-				0		0		0		0		-	
	Trabeculectomy	-				21		0		10		10		-	
Kobayashi et al. (87)	Viscocanalostomy	-		4		0	**0,0184**	0	**0,0371**	-		0	**0,0371**	0	≥0,05
	Trabeculectomy with MMC	-				20		16		-		24		8	

4.3 Discussion

In this chapter, the provided data should be interpreted. On the basis of the given figures: Which rules should be considered in the decision process? Which surgical treatment strategy should be pursued after failed trabeculectomy?

The question on the type of second surgery - penetrating or non-penetrating – is, according to my point of view, legitimately the first one. In general, non-penetrating surgery has lower impact on IOP reduction. Therefore, the targeted IOP reduction will be the main factor, whether non-penetrating surgery, that seems to cause fewer complicaticons but also seems to reduce IOP less, should be considered at all. Furthermore, non-penetrating surgery is demanding and it's not available in many hospitals. Subsequently, this approach makes sense.

4.3.1 Penetrating surgery

If decision has once been made for penetrating surgery, the next step in the decision process is to compare tube shunt surgery with trabeculectomy. Again, there are two different paths that could be followed: A surgeon might compare trabeculectomy to each one of the tube shunts or might decide together with the patient for either trabeculectomy or tube shunt surgery and afterwards, if tube shunt surgery should be performed, for the type of tube shunt. The first possibility would compare all possible procedures most equally, because each type of surgery could be decided for primarily. However, the data comparing the different types of tube shunts are not very impressive and it's hard to define the exact indications of each type. Furthermore, the tube shunt of choice might also be influenced by the surgeon's experience and his personal preference what might support the second possibility. In case of decision for the second principle, decision making would be more structured and easier to understand. Subsequently, it might be advantageous to take all tube shunts together and to decide between tube shunt surgery and trabeculectomy primarily.

With regard to the given explanation, I am going to discuss the advantages of tube shunt surgery versus trabeculectomy in the following subchapter, based on the results of the TVT. The type of tube shunt should be discussed in the next subchapter.

4.3.1.1 Tube versus trabeculectomy after failed trabeculectomy

The TVT is the only big study comparing tube shunt surgery versus trabeculectomy on patients with uncontrolled glaucoma that had previous trabeculectomy or cataract surgery or both. (3) Different studies report IOP reduction as well as complication rates either after tube shunt surgery or after trabeculectomy, but as the aim is to make a decision for one of the procedures easier, both procedures need to be compared directly. Studies reporting effects and complication rates of only one procedure aren't of that interest, as the figures highly depend on the setting. This outstanding design of the TVT explains why it is that important in the current discussion.

In how far does the TVT answer the given question? As randomised, stratified and prospective trial, the TVT provides the highest possible level of evidence. The lack of blinding should not have had a remarkable impact on the results of the TVT. Due to the fact that an implanted tube shunt can be easily detected by patients, patients must have been aware of the method they had undergone from the first beginning. However the placebo-effect should have a relative low impact on the IOP, especially if compared to the impact on pain and subjective sensations.

In the TVT, the differences in the failure rate and the rate of reoperation for glaucoma were reported to be significantly different among the two groups. (64) The cumulative probability of failure makes up 29.8% in the tube group and 46.9% in the trabeculectomy group, what means that failure was reported to be 1.57 times more frequent in the trabeculectomy group than in the tube shunt group. The hazard ration is a further parameter to put both failure rates in relation to each other, but in contrast to cumulative probability, events don't contribute equally to this parameter. The timing of an event influences its impact on the value. The ratio continues to increase for events that occur sooner. In the TVT, the hazard ratio for the failure rate was reported to be 2.15, what means that failure in the tube group occurred later than in the trabeculectomy group. (46,64)

Significantly higher failure rates for trabeculectomy were even found when failing criteria were defined more stringently, so when the target IOP was defined to be under 17 mmHg or 14 mmHg. These altered failing criteria might be of interest in case of normal tension glaucoma.

Some critics, who do not believe that the true failure rate for tube shunt surgery is that low, argue the other way round. They claim that the failure rate in the trabeculectomy group was

unexpectedly high. However, Geddy et al defend their results and argue that in the TVT, the failure rates of trabeculectomy are comparable to similar studies. (88)
Katz et al. seem to be critical about the study results as well and argue: “In the TVT, complications were not “weighed” on the same level of concern. […] Although overall complication rates favour the tube group, when the more serious sequelae are separately examined there may be more concerns in the tube shunt group.”(89) Of course, the safety profile is not only determined by the complication rate, also by the severity of complications and their possibilities to treat. Taking a look at the early postoperative complications in the TVT, those complications with higher incidence in the tube group are only minimally more frequent, what means that the above argumentation wouldn’t make sense. Situation shifts when late postoperative complications are studied closer and subsequently Katz’s statement seems to be reasonable. Persistent corneal edema, which was reported to be almost two times higher in the tube shunt group is considered as a particularly severe complication, especially if penetrating keratoplasty is required. As the tube shunt nearly always needs to be removed in case of tube erosion, this complication should be classified as severe as well. Also persistent diplopia and cystoid macular edema, also severe complications, occurred 3 and 2,5 times more frequently in the tube group. Subsequently Katz’s statement might be reasonable but still it is not evidence based. Complications like hypotony maculopathy and endophthalmitis are also severe ones and each one was reported to occur 5 times more frequently in the trabeculectomy group. Furthermore no single complication was significantly higher in one of the groups. (65)
Although complications were reported to be more frequent in the trabeculectomy group, patients in the tube group were more frequently, but not significantly more frequently, re-operated for complications. If severe complications were defined by the need for reoperation, again Katz’s assumption would be comprehensible. However, the rate of serious complications wasn’t proven to be significantly different (p-value 0.79) (65)
Interventions, procedures which do not fulfil criteria to be classified as reoperations, like laser suture lysis, removal of sutures, 5-FU injection or needling, were significantly more frequent in the trabeculectomy group, about 3 times more patients underwent them. However, due to their easy management, its increase hardly matters.
For the decision process in clinical practice, it’s important to be aware that different reasons contribute differently to the failure rates. *Table 15* shows the distribution of reasons for treatment failure in the TVT (64).

Taking the complication rates into account, complications leading to hypotony were the only ones which were found to be significantly different in the number of people being affected. In the trabeculectomy group, 12 patients with wound leak and 6 patients with bleb leak were reported. Both complications are the only reasons listed for hypotony and both are significantly higher in the trabeculectomy group. Although persistent hypotony can occur after tube surgery too (due to wound leak), it seems to be a typical complication of trabeculectomy.

One of the typical side-effects of tube surgery is diplopia, although persistent diplopia didn't reach statistical significance in the TVT. Only the incidence of postoperative motility disturbances (p-value: diplopia =0.06, motility disturbances 0.05) was significantly higher in the tube shunt group. (90)

However, patients didn't only require reoperation because of complications, they also required reoperation for glaucoma, in case of inadequate IOP reduction. Significantly more patients in the trabeculectomy group were affected. The numbers are provided in *Table 15*. However the data are not reasonable at all. In the trabeculectomy group, significantly more patients were re-operated for glaucoma, although average IOP reduction remained similar between the groups. These findings could indicate that trabeculectomy is more likely to fail for a certain subpopulation.

Before I am going to take all the results and different points of view into account, I want to deal with the more basic question "Tube versus trabeculectomy in primary glaucoma surgery" shortly. To be able to discuss this question in case of certain conditions, as in terms of failed trabeculectomy, it is important to know about the basic discussion.

> The gold standard for primary glaucoma incisional surgery is trabeculectomy. (2) M. Roy Wilson, who compared primary trabeculectomy to the primary implantation of an Ahmed glaucoma valve implant, noted lower IOPs in the trabeculectomy group during the first year of follow-up, while IOPs and postoperative complications after longer time of follow-up were found to be similar between both groups. Higher administration of IOP-reducing drugs in the tube group could subsequently be proven as significantly relevant. (91)
>
> This study was carried out in Sri Lanka and was published in 2003. The TVT was initiated four years later, the article on the five year follow-up appeared in 2012. Considering the continuous improvement of tube shunt surgery with time, Wilson's results might have dwindled in importance. A brand new study, published by Peter N.

> Netland (92) in 2014, who compared the primary implantation of the EX-PRESS glaucoma filtration device to primary trabeculectomy, provides evidence, that a development in tube surgery is taking place. IOP reduction was found to be similar in both groups, but postoperative complication rate was significantly higher after trabeculectomy. Before, in 2012, E. Dahan had found identical results in a similar setting. (93)
>
> However, in clinical practice, when decision for one of the procedures needs to be made, the effect of IOP reduction and the number of side effects are not the only parameters that influence the decision process. The possibility of further operations if a procedure has failed is a further factor that contributes heavily and that does need to be considered when deciding for the initially performed operation.
>
> After failed tube shunt surgery, the number of further procedures is limited. Trabeculectomy becomes more difficult (less space) and therefore the two remaining options are another tube shunt or laser cycloablation.(89) Relating to these benefits of trabeculectomy Jay Katz stated in 2009: "With more surgical options down the road and a better chance of attaining an ideal IOP without medications, the scale may tip in favor of trabeculectomy as the better option."

Why is this comment important for the discussion? What is the main difference between both questions? Between "Tube versus trabeculectomy after failed trabeculectomy" and "Tube versus trabeculectomy as primary glaucoma surgery"?

In the first case, when patients and doctors need to decide together for the second surgical procedure, doctors have important information, which they have missed in the previous decision process: Trabeculectomy has already failed once. This additional knowledge seems to be obvious, but needs to be pointed out due to its high relevance.

People respond differently to trabeculectomy. Intrinsic factors may influence the outcome. Specific genetic predisposition might explain why patients are differently vulnerable to bleb leak as well as to scaring. However, also the surgeon might be responsible if trabeculectomy tends to fail, for example if it is carried out inadequately.

If primary trabeculectomy fails because the patient is liable to failure, if it is assumed that trabeculectomy has failed because of a certain predisposition, a further trabeculectomy should be more likely to fail again. In this case, surgeons reasonably tend to perform tube shunt surgery, that is characterized by a bigger bleb. Simplified and expressed in an exaggerated way, someone might argue that the TVT reports success of tube shunt surgery

when trabeculectomy has been predicted to fail. Subsequently, the results from the TVT are not transferable to primary glaucoma surgery and have no impact on it. A further study, the "Primary Tube versus Trabeculectomy Study" is required and currently carried out. (88)
It is believed that the results of the TVT have caused a major shift in ophthalmologists' preferences. However, as Gedde et al. write in their review on the interpretation of the results from the TVT: "The TVT Study does not demonstrate clear superiority of one glaucoma operation over the other.", the results need to be discussed critically and limitations need to be kept in mind. (88)
To avoid side effects, surgeons are less generous in the application of antimetabolites nowadays(94) and therefore it might be that the relative high amount of MMC in the TVT caused the high rate of persistent hypotony in the trabeculectomy group. (64)
Secondly, many patients in the TVT had already failed trabeculectomy and therefore bias could have been introduced in favor of the tube group. (64)

In this chapter, the impact of trabeculectomy and tube shunt surgery on IOP reduction as well as the complication rates have been discussed. As the discussion has mainly been based on the results of the TVT, it doesn't provide general comparison of trabeculectomy with tube shunt surgery. The tube shunt used in the TVT was a 350-mm^2 Baerveldt glaucoma implant. This type is only one of many different types of available tube shunts, as previously described. Different tube shunts have a different impact on IOP reduction and show different complication rates. The variety of types may also influence the choice between re-trabeculectomy and tube shunt surgery. It is a quite challenging task to find the type of tube shunt that is the perfect one for the individual patient. An approach shall be worked out in the following subchapter.

4.3.1.2 Selection of the tube shunt

Clear criteria for the selection of the tube shunt do not exist. "To date, the selection of an aqueous drainage device has largely been decided by surgeon preference, influenced by personal experience and clinical center preference." (95) Christakis's et al. observation is still as true as it was five years ago in 2011, when the discussion of "The Ahmed versus Baerveldt Study" (95) was introduced by these words. Meanwhile the aim had been to find these clear criteria, but until today they have not been found.

So why is this task so difficult to solve? What makes it is so difficult to find a consistent approach? Zarbin's et al. explanation is that differences in the effect of the tube shunts are so small that it's especially difficult to prove them. The different study designs as well as mistakes, that have happened in some settings, shall make it difficult to compare study results and to merge one single instruction, one set of guidelines, that functions as exemplary model. (54)

Minckler et al. evaluate the current research status similarly to Zarbin et al.: According to them, none of the available devices can be marked as the better one, they all show comparable data. Agreement can only be reached on the assumption, that the size of the tube shunt plays the major role for the final success.

As already indicated, two independent question need to be distinguished for the selection of the tube shunt. The first question is about the model (Baerveldt, Molteno, Ahmed) or in a more shallow understanding, the type - valved or non-valved tube shunt – that should be used. Secondly, the size is the matter of interest. Definite findings are rare. The "Ahmed Baerveldt Comparison Study ABC" (66) and the "Ahmed versus Baerveldt Study AVB" (67) hardly changed the initial situation. The question still remains unanswered. However I am going to discuss these two questions in detail:

Valved versus non-valved tube shunts

The idea behind valved tube shunts is to regulate the outflow through the implant and to avoid postoperative hypotony. The listed results in chapter 4.2.2 show once more the inconsistency of the different papers. I will not comment the results once again, because those of the largest trials have already been presented and outcome is obvious, but I intend to point out some observations of interest and to share some thoughts.

Comparing the Ahmed valve implant with the Baerveldt implant, IOP reduction is continuously stronger in the Baerveldt groups, often significantly. More or less they are consistent. However, this finding is not that great, because it is weakened by the complication rates. Sometimes they were reported to be higher for those patients with the Baerveldt implant. This correlation between IOP reduction and complication rate makes sense, because the incidence of hypotony and its complications should increase with the drop in IOP. At this point I would like to remind the reader of the in the introduction presented image of the scale, that should visualise the balance between IOP reduction and avoidance of complications in glaucoma therapy. Furthermore it's important to call once more to mind, that the quoted studies do not refer to tube shunt implantation after trabeculectomy only. In contrast, most of them investigated primary tube shunt implantation. As the basic question hasn't yet been solved by far, there is no reliable information about my level of interest. The influence on the results, if tube shunt surgery had been the second surgical procedure, can only be assumed. I believe that the Baerveldt implant might be the better choice because trabeculectomy has once been indicated. It has a higher impact on IOP reduction than the Ahmed glaucoma valve implant which is believed to decrease IOP less than trabeculectomy does.

Up to now I have restricted myself to the comparison of the Baerveldt glaucoma implant with the Ahmed glaucoma valve implant in order to avoid confusion. However, the Molteno implant is comparable with the Ahmed glaucoma valve implant. (96)

One advantage of the Ahmed glaucoma valve implant, that hasn't been mentioned yet, is found in the installation process of the tube shunts. (97) The implantation of a non-valved tube shunt necessarily consists of two separate surgical procedures. In the first step, the tube shunt is implanted, but the tube is closed by a ligature, which is opened in the second step. The reason of this performance is to keep postoperative hypotony low, also if no mechanism limits aqueous outflow. The surrounding tissue needs time until it covers the plate and causes natural resistance until the aimed IOP is reached.

Last but not least one more remark to chapter 4.1.1: Diplopia is, as mentioned before, a typical side-effect of tube shunt surgery. Subsequently, it might be of interest whether one type of tube shunts is more liable to it. Zarbin et al. found in their systematic literature review a significantly higher incidence for diplopia in patients with the Baerveldt implant compared to patients with the Molteno- and the Ahmed valve implant. (54) Specific reasons are not given.

Are bigger tube shunts better?

This question can't be answered dichotomously. Mostly, the individual situation is very complex. Again, study results are partially inconsistent, but it seems to me that the controversial issues can be pinpointed more precisely than in the previous debate.

Britt's et al. intention (98) was exactly to answer the given question. The study protocol of their randomised and controlled trial was designed to compare the 350-mm^2 with the 500-

mm^2 Baerveldt glaucoma implant. Their setting suits for this investigative issue perfectly because any detected difference in IOP or in the complication rate needs to be caused by the difference in size, any difference due to various design is completely avoided. Most studies compare tube shunts of different sizes as well as of different models.

Britt et al. reported the smaller tube shunt to be significantly more successful. Many doctors agree with her, although in many papers, which are listed in the discussion, significant difference could not have been found. Whether superiority of the $350mm^2$ over the $500mm^2$ device is given depends on the publication read through, subsequently superiority is assumed but clearly not proven. However, nobody believes that this superiority is also valid in reverse order. While scientists regard the three different models of tube shunts more or less equally effective and safe, they agree that the $500mm^2$ device is not more recommendable than the $350mm^2$ device. My first presumption has been that the bigger tube shunt is the more successful one but it is clearly rebutted. The complications seem to overweigh the effect of higher IOP reduction. Britt (98) found higher incidence for most complications in the 500-mm^2-group, but none of them was significantly higher.

Conclusion is obvious: "There may be an upper limitation to the effect of implant size on pressure control and surgical success.", (98) is argued by Britt et al. like by many other specialists.

However, it's proven that a bottom limit exists either. A minimal size of the plate is necessary to reduce IOP effectively.

Once again I need to point out, that the previous data are based on primary tube shunt surgery. However, transferred to the period after failed trabeculectomy: Could there be any differences to think of? Personally I assume that the lower as well as the upper limit increases with time. Second trabeculectomy tends to fibrosis earlier. Subsequently the bleb could need to be bigger in order to reach the same outcome.

As explained explicitly, size as well as type of tube shunt needs to be considered carefully before implantation. However, can these two questions be ranked according to their importance? Does one of these factors, the ideal size or the ideal model, contribute more to the success? According to the presented data I conclude that the size plays the major role for success. Why? The different types nearly seem to be exchangeable, while the lower and the upper limit for the size of the tube shunt must not be exceeded in order to ensure effective IOP reduction.

Mini-tube shunts

Evaluation of mini-tube shunts remains difficult. Up to now, ophthalmologists have not reached agreement on the role that mini-tube shunts should play in the treatment of open-angle glaucoma. It has been satisfactorily proven that their IOP-lowering effect is significantly relevant, question is only raised on its extent. Subsequently comparison to other interventions, most important to trabeculectomy, is difficult.

The data for the Express mini-shunt, presented in chapter 4.2.2.2, reflect the deviation of the study results. In order to show the inconsistency of the results, *Table 19* does only include exemplarily studies. Compared to trabeculectomy, IOP is once shown to be significantly lower in the mini-shunt group, once proven to be significantly higher, although many studies cannot report a significant difference at all. Situation is similar if complication rates are studied closer. Many authors believe that the implantation of mini-tube shunts is favourable because of its low complication rate, especially for early postoperative hypotony and its consequences. Disappointingly, significantly lower rates have often not been found, although some authors could have confirmed them. At least, the tendency towards lower complication rates for mini-tube shunt surgery could have been reported often if difference was not significant.

All in all, mini-tube shunt surgery seems to be comparable to trabeculectomy. This reason might explain the lack of impressive results. Subsequently indications for mini-tube shunt surgery are similar to the ones of trabeculectomy, although it is by far not that popular in clinical practice. If success rates of two interventions are similar, the surgeon’s preferences play a more important role in the decision process. If experience with these devices is not given, implantation should not be carried out as success rates commonly go down.

The evaluation of the iStent causes difficulties as well. I could not find one single study comparing this type of mini-tube shunts with trabeculectomy. However, again IOP reduction is proven, although it seems to be less. “Pressure-lowering effects of this device are not comparable to traditional incisional glaucoma surgery.”(99) Wellik et Dale estimate the effect of IOP reduction after implantation of an iStent to be 3-10% higher than after cataract surgery only, although IOP reduction is significantly increased if more iStents are implanted. The figures presented in *Table 20* prove this additional effect.

I could not find one setting, in which the role of mini-tube shunts is investigated after failed trabeculectomy. However, this lack of data should not imply that they should be only considered as primary surgical treatment.

4.3.2 Non-penetrating surgery

Patients who fail penetrating surgery due to distinct wound healing are even more likely to fail again because of triggered scaring. Subsequently they are poor candidates for all kinds of surgery with conjunctival bleb formation. (100) In order to avoid the construction of a bleb that might tend to fibrosis, non-penetrating surgery, especially viscocanalostomy and trabectome surgery, has been developed. It is also offered to patients which do not fit for secondary trabeculectomy as further treatment option. Deep sclerectomy is bleb-forming as well, but the natural pathway remains intact.

Up to now non-penetrating procedures have been beyond the scopes of this discussion, but now its horizon is broadened and the discussion is extended to the whole field of surgical procedures. First of all, I intend to go one step back. Instead of asking “Which one of the specific non-penetrating procedures is the best for patients that have failed trabeculectomy?” the question of interest should be: “Does a patient benefit more from penetrating or non-penetrating surgery?”. This systematic approach makes sense. First of all some patients which do only benefit from a very high drop in IOP, are not suitable for non-penetrating surgery. Subsequently, the question on the specific non-penetrating procedure is not asked at all. Secondly, non-penetrating surgery is by far not that popular as penetrating one and is often not offered. Of course, patients that might benefit should be transferred to a centre but in clinical practice this often does not happen.

However, the subsequent discussion is of special interest because a shift is taking place. Non-penetrating procedures are performed more and more often and new principles are introduced.

There is a lack of papers examining the role of non-penetrating surgery after unsuccessful penetrating procedures. Subsequently, the answer isn’t given by summarising the existing papers, an approach needs to be achieved in small steps. First of all, I am going to deal with the results of the two papers presented in chapter 4.2.3.1. These are the only ones I could find that directly refer to non-penetrating surgery after penetrating procedures. As they only prove success of non-penetrating surgery, but do not set them in relation to trabeculectomy

– a treating ophthalmologist is not interested in the probability of success for a single special method, he wants to know which one of the procedures achieves the better results – studies comparing non-penetrating surgery with trabeculectomy after failed trabeculectomy are required, but this issue should be discussed afterwards.

To assess a surgical procedure, two factors need to be evaluated: The achievement of the surgical treatment goal (IOP reduction in the current situation) and the observed complication rate. The expectancy of these two parameters results in the decision for final treatment.

Both of the mentioned studies prove efficiency of non-penetrating surgery: "DS [deep sclerectomy] with MMC appears to be a safe and effective surgical procedure for eyes with previous intraocular surgery.", states Anand (79) justifiably in the conclusion of his paper. The reduction in IOP as well as the decrease of glaucoma medication was proven to be statistically significant after deep sclerectomy. Also Mosaed (63), who examined the impact of trabectome surgery after failed tube shunt surgery, reported a significant IOP reduction, although reduction was not high enough to prove a significant decrease in the number of required antiglaucoma drugs.

Non-penetrating surgery has continuously been developed because of its good safety profile in comparison to trabeculectomy. Data is presented in *Table 24* (chapter 4.2.3.2). For instance, hypotony was observed in 6,1% (Anand, follow-up 5 years) and 10% (Mosaed) of the patients, while the five year follow-up in the TVT reports an incidence of 15,5% in the trabeculectomy- and of 4,29% in the tube shunt group. 2007, Rebolleda (101) reported even better rates for deep sclerectomy in a very similar setting. However, prove is not given because direct comparison is not offered. Furthermore, the design of both studies is retrospective and subsequently it raises some limitations concerning interpretation. For instance, causality isn't given in retrospective studies. Also bias needs to be considered.

These two studies show limitations and only investigate the efficiency of one single method after failed trabeculectomy. In order to prove superiority or non-inferiority over trabeculectomy, non-penetrating surgery needs to be compared to trabeculectomy. As I could not find papers investigating non-penetrating surgery versus trabeculectomy after failed trabeculectomy, I need to discuss this issue one level lower on the basis of the existing literature (primary non-penetrating surgery versus primary trabeculectomy). Afterwards I will transfer the conclusion into the level of interest, in an attempt of generalisation.

As before, I'm going to concentrate on IOP reduction firstly. In *Table 23* the relevant studies are summarised. As non-penetrating surgery was developed to improve the safety profile of glaucoma surgery, nobody expects it to be by far more effective in lowering IOP. Thus the aim is to prove that decision for non-penetrating surgery does not compromise effectiveness. *Table 23* doesn't include each single existing survey, but summarises the most important ones. In only three studies, two on viscocanalostomy and one on deep sclerectomy, the difference in IOP (between the two groups) is statistically significant and depicts deficiency of non-penetrating surgery. All other studies provide comparable results regarding efficiency. Some studies also provide contrarily information.

However, non-penetrating surgery would not obligatorily loose in importance if it lowered IOP less than trabeculectomy. It could be argued that even if non-penetrating surgery is less effective, lower efficiency might be accepted for some patients gladly if therefore complication rate is improved. The patient population that might benefit from this shift in risk distribution should be discussed later on, primarily I need to take a closer look at the actual complication rate and for this purpose again *Table 24* is of interest. I am going to refer to all single complications presented in chapter 4.1.2 with focus on their frequentness, their pathophysiology as well as their treatment:

- Inflammation: Many surveys don't provide information about the incidence of inflammation. Mermoud et al. (81) reported a significantly higher incidence of inflammation in the trabeculectomy group. This result might be expected because the anterior chamber isn't entered for deep sclerectomy. Thus the incidence and the severeness of inflammation, especially of endophthalmitis, should be lower for non-penetrating surgery.
- Perforation of the trabeculo-Descemet's-membrane only occurs after non-penetrating surgery. According to the results in *Table 24*, it was reported to be between 2% and 24%. However, during the surgeon's first 10-20 operations, Mendrinos et al. (59) estimate the rate of perforation to be even around 30%, but the long learning curve is common knowledge.

  Hypotony may logically follow perforation. However, clinical trials clearly show that hypotony is by far the bigger problem of trabeculectomy than of non-penetrating surgery. I couldn't find a single study reporting hypotony more often for non-penetrating surgery than for trabeculectomy. The difference is mostly proven to be statistically significant. The perforation of the trabeculo-Descemet's-membrane seems to be managed solidly by conversion into trabeculectomy, at least for the prevention of hypotony. Analogously, the consequences of hypotony, like flat anterior chamber and choroidal detachment are continuously reported to be quite rare after non-penetrating surgery. In the reported studies, these two consequential complications had always higher rates in the trabeculectomy group, sometimes significantly higher ones. However, also if the difference hasn't been reported to be statistically significant, difference doesn't need to be small. The power of a study, thus the size of it, is designed to be able to prove the statistical significance for the primary outcome. The power doesn't target the secondary outcomes of a survey. They might be found to be statistically significant, or not, also if they actually are.

- Hyphema, cataract: Incidences for these complications are similar. The rate for hyphema as well as the one for cataract is higher in the trabeculectomy group, partially significantly. In the provided data, Carassa et al. (84) are the only ones who fall out of alignment, reporting a higher rate of hyphema in the viscocanalostomy group.
- Egrilmez et al. (102) investigated the impact of glaucoma surgery on astigmatism. He reported a significantly higher rate for trabeculectomy after some months of follow-up.

All trials agree on the beneficial and excellent safety profile of non-penetrating surgery if compared to equal procedures. I could only find one statement of disagreement with this widely acknowledged point of view. Mendrinos et al. (59) wrote that this low incidences of complications after non-penetrating surgery are only true for the early complications. The late complications should have a similar incidence if compared to trabeculectomy, because they mainly result from excessive scarring, which isn't influenced by the type of surgery. Personally, I can't verify this quotation. No explanation refers directly to it and the quoted papers don't provide consistent results. In contrast, many of them seem to be in contradiction to this statement. For instance, progression of cataract definitely counts to the group of late complications and not one of the studied papers reports higher rates for non-penetrating surgery. Furthermore, Egrilmez (102) disagrees completely when astigmatism is taken into consideration. Mendrinos et al. mentioned a prospective comparative study reporting greater central corneal damage after trabeculectomy than after deep sclerectomy and Arnavielle et al. (103) reported significantly higher endothelial cell loss after trabeculectomy than after deep sclerectomy and concluded that corneal damage needs to be lower.

Following these results, the generalised statement that the rate of late complications is the same for both types of surgery should be considered critically.

To sum up, trabeculectomy might reduce IOP in some patients more effectively. However, patients do benefit from the good safety profile of non-penetrating surgery. Thus, it might be recommended especially to patients who are liable to complications. Furthermore, non-penetrating surgery might be especially useful for patients with mild glaucoma, whose IOP doesn't need to reach particularly low values. They could benefit from its good safety profile. Subsequently, non-penetrating surgery might play an earlier role in the disease process than all the other surgical procedures. (61) However, I need to mention that the follow-up time of the studies is mostly low. If success of non-penetrating surgery actually lasts shortly, non-penetrating surgery should be stalled.

Up to now, I have compared non-penetrating surgery with trabeculectomy as the first surgical method being performed. As this essay is about therapy options after failed trabeculectomy, the preceding discussion needs to be converted to the level of interest. I have chosen this approach as there are no papers available that investigate this issue. Subsequently the following discussion and conclusion is not evidence-based and is based on plausible thinking. However, this limitation doesn't devalue the subsequent part as this one is highly clinically relevant and corresponds to common clinical practice.

To discuss the role of non-penetrating surgery after failed trabeculectomy, I need to deal with the role of wound healing after trabeculectomy because this healing process makes the main preoperative difference between primary and secondary non-penetrating surgery.

What's the situation for trabeculectomy? Secondary trabeculectomy has a lower success rate than primary one. (100) Yet it has not completely been solved whether primary trabeculectomy is - next to the well-known general risk factors - an additional risk factor for secondary trabeculectomy or whether secondary trabeculectomy has a lower success rate because the well-known risk factors increase in their impact during the time bridged by primary trabeculectomy. (The number of medications and laser treatments increase with time.) Primary trabeculectomy itself is considered to be an additional risk factor by many authors but couldn't be proven to be. For example, Broadway et al. reported – as expected- a significantly higher failure rate for secondary trabeculectomy, but after matching all the other risk factors, failure rate did still remain higher for secondary trabeculectomy, although not significantly. (100)

The decrease in IOP reduction is caused by the healing process after failed trabeculectomy that causes bleb failure. This scaring occurs in the first months post surgery. (100) Ophthalmologists agree that the conjunctiva and the Tenon's capsule are the structures most liable to scarring, the sclera as well as the cornea are characterised by a low cell metabolism and hardly proliferate after surgery. Subsequently the conjunctiva and the Tenon's capsule are the structures of interest in the current context.

How do the conjunctival cells exactly react due to conjunctival incision? Broadway et al. deliver some data. (100) He made two observations: At the opposite side of primary surgery, he detected, compared to the control patients, which haven't undergone surgery yet, an increased number of fibroblasts and lymphocytes in the substantia propria of the conjunctiva. At the side of surgery he found less fibroblasts.

What might these results indicate? Conjunctival incision does activate all conjunctival fibroblasts, independent from their localisation, although, during the scaring process, the fibroblasts on the side of surgery become fewer and fewer and are replaced by extracellular matrix. Different substances are discussed to interfere with the fibroblast, like lens proteins, cytokines, and other molecules that are dissolved in the aqueous humour. Its composition as well as its flow speed and its direction plays an important role. (104) Furthermore conjunctival sutures and conjunctival predisposition should also play an important role. (105) The given information refers to trabeculectomy only, although I can't make up a reason why it should not be valid for tube shunt surgery as well.

As there is agreement that the conjunctiva and the Tenon's capsule are mainly responsible for scaring, non-penetrating surgery, at least the non-bleb forming one, seems to be advisable after failed trabeculectomy. If trabeculectomy actually is an additional risk factor it would make sense to perform a method, whose success is independent on the healing process of the conjunctiva.

However, is there any other reason that might reduce success of non-penetrating surgery if it is performed secondarily? Rohen et al. (106) reported from his animal experiment with monkeys that trabeculectomy has mostly been covered by endothel. As non-penetrating surgery aims to improve the natural aqueous outflow via the Schlemm's canal, primary trabeculectomy might also reduce the success of non-penetrating surgery. A second reason could be that the Schlemm's canal is damaged by trabeculectomy resulting in a poorer outcome of non-penetrating surgery. Due to a lack of studies it's unknown whether these observations are clinically important.

4.3.3 Preference to surgery

Up to now, I have presented and discussed the surgical and the non-surgical treatment options for the chronic open-angle glaucoma and have compared each treatment option to the other ones of the subgroup. If available, I have discussed the treatment options upon published trials carried out after failed trabeculectomy, and if not, I have compared the available data and have speculated on the differences that could appear if the trials had been carried out on patients with a history of failed trabeculectomy.

I have discussed the surgical treatment options after the non-surgical ones. As explained in the introductory chapter, this order is not coincidental: The duration of the surgical success is limited for nearly all kinds of glaucoma surgery and therefore decision for surgery needs to be made carefully. Hence, medical and laser treatments need to be considered prior to any surgical intervention. Mostly, ophthalmologists will even try to avoid surgery as long as possible. The non-surgical interventions will mostly be favoured to the surgical ones. This kind of preference is what I called the non-surgical approach in the introductory chapter. It is some kind of reluctance that arises from clinical experience and know-how. It is not always evidence-based and does not mean that ophthalmologists have prejudice against surgery. This term would be too strong because it would indicate that ophthalmologists put surgery unjustifiably at disadvantage and this is certainly not true. Ophthalmologists may just try to delay surgery because they know that the duration of its success is limited. Hence this non-surgical approach is justified, but, of course, not without conditions. It is only good for patients that are believed to take benefit from it. However, there are also patients who are more likely to benefit from an early surgical intervention and these patients should be treated upon the surgical approach. Numerously, they are much fewer but they still need to be identified from the very beginning. The moment that is marked with the green arrow in the figure represents the one at which decision needs to be made for one of the two approaches. The factors on which the decision should be made should be identified immediately. However, before I want to explain why it is reasonable to me to distinguish between these two approaches. Some people might argue that this does not make sense because all treatment options should be compared to all, without making any difference

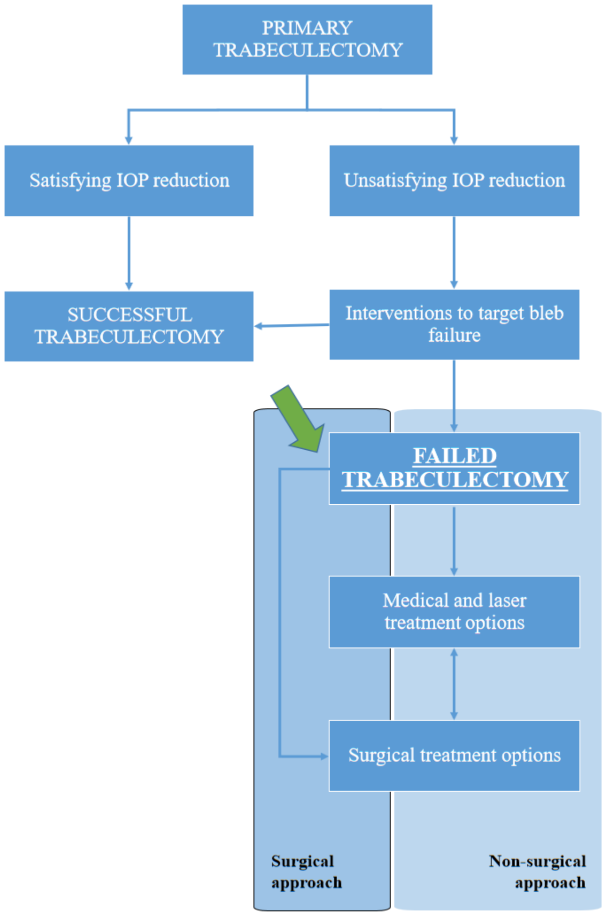

Figure 7: Different approaches in glaucoma therapy.

whether it is a surgical or a non-surgical one. This point of view seems to be plausible to me too but simultaneously this concept seems to be idealistic. It's simply not possible to develop a study design in which all treatment options are compared to each other equally and therefore it does make sense to set up two main approaches which are subdivided into further ones.

Now, what's the main difference for the individual patient? What's the difference between a surgical and a non-surgical intervention? First of all, the potential to reduce IOP. If the results presented in chapter 3.2 and 4.2 are compared according to the measured IOP reduction, the reported IOP reduction ranges from 10 to 15mmHg in chapter 4.2 (surgery) and is continuously higher than the IOP reduction reported in chapter 3.2 (medical and laser treatment), ranging from 5 to 10mmHg. Hence, surgery has a higher potential to reduce IOP. There are only two exceptions: cyclophotocoagulation and mini-tube shunt surgery. Cyclophotocoagulation is predicted to reduce IOP by 10 to 15mmHg and is therefore comparable with surgical interventions. In contrast, mini-tube shunt surgery is, if compared to other surgical interventions, less effective, and reduces IOP by 5 to 10mmHg only. This observation should be discussed closer in the second next paragraph. Before, the factors that influence whether a patient should be treated upon the surgical or the non-surgical approach should be identified. In the Second Consensus Meeting, the following indications for early surgery have been listed by the "World Glaucoma Association". (107) Glaucoma being refractory to medical and laser treatment is of course an indication for surgery but is not in the list below because this is about the indications for early surgery:

- Poor compliance
- "Progression of glaucoma, considering both, the structural and functional integrity of the optic nerve […]"
- "Patients with damage threatening central vision"
- Long life expectancy and young patients
- "Fellow eye vision loss from glaucoma"

Under these conditions, surgery should be considered earlier. They might help to decide whether the surgical or the non-surgical approach should be favoured. All these patients that are treated upon the surgical approach have in common that they are in need for high and prompt IOP reduction.

Prior to drawing the final conclusion of this essay, I need to query the definition of surgery. By assigning each method either to chapter 3 or 4, I classified each method as a surgical or a non-surgical one. However, can an intervention be classified as either a surgical or a non-surgical one? Some interventions yes, but clearly not all because definitions are not always definite. If surgery is defined as an invasive procedure, all laser treatments, apart from ECP, would be non-surgical procedures and ECP would be a surgical one. Nevertheless, I discussed ECP in chapter 3 and therefore classified it as non-surgical because the level of invasiveness is low, the surgical skills that are required are fewer than for all other surgical procedures and its relation to TCP is close. However, if the definition of cyclophotocoagulation, even TCP, is not based on the description as a process, but if it's based on its effect, cyclophotocoagulation bears resemblance to surgery because its potential to reduce IOP is comparable to the one of surgery. This functional approach, meaning that all the interventions are classified by their impact on IOP and not by their technique, so the ambiguity of this definition, needs to be remembered if decision for surgery is made. Subsequently, cyclophotocoagulation could be one alternative to the discussed surgical interventions and, the other way round, if ophthalmologists decide against surgery, cyclophotocoagulation would not be the first choice. Yang et al. (108) published a meta-analysis and they could not find statistical difference between ECP and alternative surgeries for refractory glaucoma. Schaefer et al. (109) compared cyclophotocoagulation to the implantation of a second glaucoma drainage device. They reported that failure of cyclophotocoagulation occurred, if it happened at all, mostly within the first two years and that cyclophotocoagulation mostly remained effective if it did not fail within the first two years, while a second tube shunt device tended to fail after 6 years. These trials could help to assess the role of cyclophotocoagulation in clinical practice properly.

5 CONCLUSION

The treatment of the chronic open-angle glaucoma is characterised by the very high number of treatment options and all of them are still available after failed trabeculectomy. Direct comparison of all the different options is difficult because some are very similar, in their impact on IOP as well as in their complication profile, and due to their high number it makes sense to divide them into three subgroups and to compare them primarily within each subgroup. Secondly, I has been explained that the distinction between different approaches makes sense and the question on the type of approach has been tackled. Thirdly, I have relativised the previous categorisation and mentioned that the classification into surgical and non-surgical treatment options should not be understood as definite division and that transitions between the different groups are smooth.

The following section should be seen as an attempt to summarise the presented results:

At very beginning, the failure of trabeculectomy needs to be confirmed and if it is irreversible and bleb massage is not successful, scleral flap suture manipulation is the option of choice. The application of antimetabolites is preferred to treat early bleb failure while Nd:YAG goniopuncture and needling is still recommended to treat late bleb failure.

If a person is believed to benefit from the non-surgical approach, if IOP does not need to be reduced immediately, medical and laser treatment are the option of choice. The different pharmacological agents might be applied together – a combination up to three agents is possible. Additionally, laser treatment might be administered, either if medical laser treatment is not sufficient or if one of the indications that are discussed in chapter 3.3.2, like poor compliance, is present. Trabeculoplasty might be the option of choice in a relatively early stage of glaucoma and can be repeated if done with the Nd:YAG laser. Cyclophotocoagulation might be used if IOP reduction needs to be high and prompt, can be repeated as well and might be carried out endoscopically, especially if done in combination with cataract extraction. Surgery is indicated if glaucoma is refractory to medical and laser treatment options and primarily if the surgical approach has been chosen. After failed trabeculectomy, all kinds of surgery are possible but tube shunt surgery might be beneficial to further trabeculectomy, although some ophthalmologists strongly doubt this widespread point of view. The impact of the different types of tube shunts is similar. The size of the tube shunt seems to be important and a lower and an upper limit seem to exist and it must not be exceeded if IOP control should be effective. The role of mini-tube shunt surgery is still discussed controversially because the extent of IOP reduction remains unclear, but it seems to be comparable with trabeculectomy. However, for sure, clinical experience is important. Non-penetrating surgery does not seem to have the same potential to reduce IOP, its impact on IOP is considered to be a bit lower than the one of penetrating surgery, but nevertheless, it is a promising intervention especially due to its great safety profile. If the conjunctiva and the Tenon's capsule tend to fibrosis, it is, at least theoretically, a good idea to keep surgical success independent from the conjunctival behaviour and to increase the outflow of the natural filtering pathway.

5.1 Final statement

Different ophthalmologists have their own personal approaches to treat the chronic open-angle glaucoma and the very high number of different treatment option is responsible for the development of a wide range of different and successful treatment strategies. The true and only one does not exist. The adaptation to the individual patient seems to be the major factor of success and hence, clinical experience is essential to achieve an appropriate IOP control. Like mentioned previously, the success of each treatment option depends on the skills and the experience of the person in charge.

Physicians generally long for one general instruction and universal guidelines but this desire has not been fulfilled in the course of time, it still seems to be out of reach and therefore continues to inspire people to develop new treatment strategies and individual paths to success.

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