SLT versus ALT in Glaucoma Patients Treated Previously with 360-degree SLT—A Randomised, Single-Blind, Equivalence Clinical Trial

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Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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Abstract

Our objectives were to compare the efficacy and safety between selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) for the open-angle glaucoma patients who had 360-degree SLT previously and to explore the baseline predictors for the treatment success. Data were obtained from a multicenter, patient-masked, randomised, parallel-group, active-controlled trial. The enrolled patients were randomly assigned to receive either SLT or ALT. At 12-month follow-up, the mean intraocular pressure (IOP) reduction was 3.35 mmHg and 3.36 mmHg after SLT and ALT respectively. The difference of mean IOP reduction was -0.01 mmHg (n=115). The 95% CI of the difference was between -1.86 to 1.84 mmHg and was within the predetermined equivalence margin (-3 to +3 mmHg). Baseline IOP and number of glaucoma medication were significant predictors of treatment success (OR, 1.19 and 0.63). The findings suggest that although SLT had an equivalent IOP-lowering effect as ALT after the failure of 360-degree SLT, repeat laser treatments had a lower efficacy than the primary ones.

Keywords

Argon laser trabeculoplasty, equivalence, intraocular pressure, predictor, randomised controlled trial, selective laser trabeculoplasty.
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# List of Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAs</td>
<td>alpha-agonists</td>
</tr>
<tr>
<td>ACG</td>
<td>angle-closure glaucoma</td>
</tr>
<tr>
<td>ALT</td>
<td>argon laser trabeculoplasty</td>
</tr>
<tr>
<td>AUC</td>
<td>area under curve</td>
</tr>
<tr>
<td>BBs</td>
<td>beta blockers</td>
</tr>
<tr>
<td>BCVA</td>
<td>best-corrected visual acuity</td>
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<tr>
<td>CAIs</td>
<td>carbonic anhydrase inhibitors</td>
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<tr>
<td>CCT</td>
<td>central corneal thickness</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>FDA</td>
<td>the US Food and Drug Administration</td>
</tr>
<tr>
<td>IOP</td>
<td>intraocular pressure</td>
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<tr>
<td>OAG</td>
<td>open-angle glaucoma</td>
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<tr>
<td>OD</td>
<td>oculus dexter (right eye)</td>
</tr>
<tr>
<td>OHT</td>
<td>ocular hypertension</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>OS</td>
<td>oculus sinister (left eye)</td>
</tr>
<tr>
<td>OU</td>
<td>oculus uterque(both eyes)</td>
</tr>
<tr>
<td>PDS</td>
<td>pigmentary dispersion syndrome</td>
</tr>
<tr>
<td>PGAs</td>
<td>prostaglandin analogues</td>
</tr>
<tr>
<td>POAG</td>
<td>primary open-angle glaucoma</td>
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<tr>
<td>PXF</td>
<td>pseudoexfoliation syndrome</td>
</tr>
<tr>
<td>PXG</td>
<td>pseudoexfoliative glaucoma</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised clinical trial</td>
</tr>
<tr>
<td>RD</td>
<td>risk difference</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver-operating characteristic</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SLT</td>
<td>selective laser trabeculoplasty</td>
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Chapter 1 Introduction

This chapter includes five sections. Section 1 describes the background knowledge of primary open-angle glaucoma, secondary open-angle glaucoma, and ocular hypertension. Section 2 explains the rationale for this study. Section 3 constructs the goal and objectives of the study. Section 4 presents the data resources and my role in the study. Section 5 provides an outline of this thesis.

1.1 Background

Definition and classification of glaucoma

Glaucoma is a type of optic neuropathy with characteristic progressive degeneration and functional deterioration of the optic nerve, including the retinal nerve fibre layer and optic nerve head, leading to visual field loss and even blindness.\(^1\)\(^2\) Based on the appearance of the iridocorneal angle, glaucoma is divided into angle-closure glaucoma (ACG) and open-angle glaucoma (OAG), both of which can be subdivided into primary or secondary based on without or with ocular or systemic causes.\(^3\)\(^4\)\(^5\) In primary open-angle glaucoma (POAG), the iridocorneal angle is wide and open (unobstructed) with normal appearance, but aqueous outflow is diminished.\(^5\) The intraocular pressure of POAG can be high or normal.\(^6\) Examples of secondary OAG includes pseudoexfoliation syndrome (PXF) related glaucoma and pigmentary dispersion syndrome (PDS).\(^5\) In this thesis, POAG, PXF and PDS were studied. Besides, ocular hypertension (OHT), was also included to generalize the study population.

Epidemiology of POAG

- Prevalence of glaucoma

Glaucoma was the first leading cause of irreversible blindness globally in 2002 according to the latest data.\(^7\) It is estimated that there will be 76 million people with glaucoma in 2020 and the number will rise to 111 million in 2040 owing to an aging population.\(^8\) POAG will account for around 70% of all types of glaucoma worldwide.\(^8\)\(^9\) According to the self-report surveys described by Perruccio et al., in 2002-2003, it was estimated
409,000 Canadians had glaucoma.\textsuperscript{10}

- **Risk factors of POAG**

  **General risk factors of POAG**

  The prevalence and progression of OAG increased with \textbf{age}.\textsuperscript{11,12} It has been consistently found that a higher prevalence of OAG in persons who are \textbf{African-derived (black)}.\textsuperscript{11} A \textbf{family history of OAG}, specifically the first-degree relatives (parent, sibling, or child) has been confirmed to be a strong risk factor for OAG in several studies.\textsuperscript{13}

  **Ocular risk factors of POAG**

  **Intraocular pressure (IOP)**

  The major risk factor for glaucoma is intraocular pressure (IOP).\textsuperscript{3} Previous prevalence surveys and longitudinal studies showed a consistent dose-response relationship between IOP and the incidence as well as progression of glaucoma.\textsuperscript{13} Several randomised controlled trials (RCTs) also confirmed IOP-lowering treatments can decrease the incidence or progression of glaucoma.\textsuperscript{14,15,16}

  In the Baltimore Eye Survey\textsuperscript{17}, the prevalence of POAG increased with the score of the screening IOP. Compared with eyes which had an IOP lower than 15 mmHg, the relative risk was 12.8, 39.0, and 40.1 respectively in eyes which had an IOP between 22 to 29 mmHg, between 20 to 34 mmHg, and 35 mmHg or above. The results of the Early Manifest Glaucoma Trial showed that on average, the estimated risk of the progression of OAG decreased by 10% with each 1 mmHg reduction of the baseline IOP.\textsuperscript{12}

  **Myopia**

  Evidence has shown the association between myopia, especially high myopia, with OAG through case series, case-control studies, and large population-based prevalence surveys. These have reported the elevation of the prevalence of OAG in people with myopia between 48% to 70% after adjusting for age and sex.\textsuperscript{13} However, The Blue Mountains Eye Study found a significant but non clinically meaningful IOP difference (0.45 mmHg) between myopic eyes and non-myopic eyes and described that structural and genetic characters in myopic eyes may contribute to the association between myopia and glaucoma.\textsuperscript{18}
**Others**

Both the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Trial showed central corneal thickness was a predictor of development and progression of OAG.\(^{19,20}\) Exfoliation syndrome was associated with progression of OAG in the Early Manifest Glaucoma Trial.\(^{20}\)

**Systemic risk factors of POAG**

**Blood pressure**

The meta-analysis of Zhao et al. summarised 60 observational studies and identified that the positive association between blood pressure and IOP were consistent and robust: on average, increasing systolic blood pressure by 10 mmHg increased IOP by 0.26 mmHg and increasing diastolic blood pressure by 5 mmHg increased IOP by 0.17 mmHg.\(^{21}\) Low blood pressure, by contrast, was shown to be a risk factor for progression of glaucoma in the Early Manifest Glaucoma Trial, and the negative association may be due to the reduction of ocular perfusion pressure caused by low blood pressure.\(^{20}\) Therefore, it was suggested that the relationship between blood pressure and glaucoma is U-shaped.\(^{22}\)

**Diabetes**

Although some studies suggested that people with diabetes have a higher risk of OAG, it has not been a consistent finding.\(^{23}\) The association might be confounded by IOP.\(^{23}\) Besides, lack of standard definition of diabetes among articles is another reason for the discrepancy in conclusions.\(^{23}\) The Baltimore Eye Survey showed that diabetes patients tended to have a higher IOP, but they did not have a greater risk of OAG.\(^{24}\)

**Others**

The relationship between cerebrospinal fluid and glaucoma is not well understood. Studies have shown that the increase of the pressure difference between IOP and the orbital cerebrospinal fluid pressure was a possible risk factor for glaucoma.\(^{25}\) Similar to diabetes, evidence of the association between glaucoma and other systemic diseases, such as migraine, thyroid disorders, sleep apnea, and cardiovascular disease, is not consistent or not sufficient.\(^{23}\)
Figure 1: Formation and circulation of the aqueous humor.

The diagram shows the anterior segment of the eye. Aqueous humor, produced in the ciliary body, circulates through the pupil into the anterior chamber, passes through the trabecular meshwork into Schlemm’s canal, and finally, drains into the episcleral venous system. Reproduced with permission from Kwon, Y. H., Fingert, J. H., Kuehn, M. H. & Alward, W. L. M. Primary open-angle glaucoma. N. Engl. J. Med. 360, 1113–24 (2009), Copyright Massachusetts Medical Society.

Pathology and mechanism of POAG

Although the pathogenesis of POAG has not been fully understood, elevated IOP is considered an important causative factor of POAG. Aqueous humor, which has multiple physiologic functions for the eye, is produced at the ciliary body. The most important outflow pathway by which the aqueous humor leaves the eye is through the trabecular meshwork located at the iridocorneal angle (Figure 1). IOP is normal when the circulation is balanced. For whatever reasons, reduction of aqueous outflow through trabecular meshwork elevates IOP. In OAG, IOP elevation is due to the increased resistance of aqueous drainage through the trabecular meshwork. By contrast, the access to the trabecular meshwork outflow pathway is obstructed by the iris in angle-
closure glaucoma patients. Increased IOP causes extra mechanical stress and strain in all compartment of the eye, notably the lamina cribrosa (the collagen support tissue of the optic nerve) and adjacent tissue, and increases the probability of progressive damage of the optic nerve head. In normal tension open-angle glaucoma, the glaucomatous optic neuropathy may be caused by a large pressure gradient across the lamina cribrosa due to an abnormally low pressure of cerebrospinal fluid in the optic nerve subarachnoid space.

Independently or in addition to IOP, other factors may individually or collectively cause the loss of retinal ganglion cells followed by the atrophy of the optic nerve fibres. Those factors include vascular dysfunction in the retina, autoimmune-mediated nerve damage, excessive stimulation of the glutamatergic system, poorly functioning cellular pumps and glutamate transporter, oxidative stress and subsequent free radicals formation, some inflammatory cytokines, and abnormal immunity.

Clinical presentation and diagnosis of POAG

In general, POAG is a chronic, binocular disease. The progression between two eyes may be asymmetric, with one eye having more adversely affected optic neuropathy than the other. Due to the asymptomatic nature of POAG, several population-level surveys found that up to 50% of people with glaucoma were unaware of the disease until recognizable vision loss when they were examined. Diagnosis of POAG is made with open and normal iridocorneal angle, detection with the excavation of the optic nerve head, thinning of the retinal nerve fibre layer, and narrow neuroretinal rim.

Darkroom gonioscopy is used to observe the anterior chamber angle to discriminate between open-angle and angle-closure glaucoma. In either type of glaucoma, the neuroretinal rim becomes narrow with concomitant enlargement of the cup. The assessment of optic nerve head includes subjective and objective ways. To gain a stereoscopic view, the subjective examination, which is evaluated by an ophthalmologist, should be performed at a slit lamp biomicroscope with an indirect lens or contact lens, rather than a direct ophthalmoscope. Several objective quantitative technics commonly used in the medical clinics include scanning laser polarimetry, confocal scanning laser
ophthalmoscopy, and optical coherence tomography (OCT). OCT is now the most commonly used test. An indirect test used is the visual field.

Diagnosis of POAG does not require visual field loss because it usually happens after the damage of the optic nerve head and the retinal nerve fibre layer. However, perimetry is an important tool for the recording and monitoring the functional decline due to glaucoma. Similarly, elevated IOP is not a diagnostic requirement of glaucoma. Several population-based studies found that up to 50% of glaucoma patients had an IOP lower than 22 mmHg. Since IOP is a major risk factor for glaucoma, it is used to predict the progression of glaucoma. Various contact and non-contact tonometers are available for IOP test. Goldman applanation tonometry is considered the most widely adopted approach.

**Treatment of POAG**

The goal of POAG treatment is to preserve vision by lowering IOP, which can be achieved by glaucoma medication, laser therapy, and surgery. The five contemporary classes of medication in use include prostaglandin analogues (PGAs), beta-blockers (BBs), carbonic anhydrase inhibitors (CAIs), alpha-agonists (AAs), and cholinergic. Besides those single topical ocular hypotension agents, some fixed combination therapies are available in Canada, including Cosopt (combines a beta-blocker and a CAI), Combigan (combines a beta-blocker and an alpha-agonist), DuoTrav (combines a prostaglandin analogue and a beta-blocker), and Xalacom (combines a prostaglandin analogue and a beta-blocker). The most common types of laser treatment for open-angle glaucoma are argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT). Incisional glaucoma surgery is not considered as the primary treatment in most settings due to the potential risks of severe complications.

- **Glaucoma medication**

  **Prostaglandin analogues**

  The IOP-lowering effect of prostaglandin analogues (PGAs) is achieved by improving uveoscleral outflow (the second most important outflow channels after the trabecular meshwork). The possible mechanisms include relaxation of the ciliary muscle and
remodeling extracellular matrix of the ciliary muscle as well as sclera. Latanoprost, bimatoprost, travoprost, unoprostone, and tafluprost are the five commercially available PGAs, and the first three types of PGAs are the most commonly used in clinical practice. All of them reduce IOP by around 30%. The systemic adverse effects are rare for PGAs. The common local adverse effects include conjunctival hyperemia, eyelash growth, and periorbitopathy. In general, the PGAs are well tolerated, and less than 5% of patients discontinue to use them as a result of side effects.

**Beta-blockers**

Beta-blockers (BBs) have been the mainstay of glaucoma medication for decades since their introduction in 1978. The mechanism of IOP-lowering effect is suppression of aqueous humor production via the blockage of β-adrenoreceptors in ciliary epithelium cells. The suppression was observed using fluorophotometry in humans. There are two types of BBs including nonselective β1 and β2 antagonists along with selective β1 antagonists. The nonselective type includes timolol, levobunolol, metipranolol, and carteolol. Betaxolol is a selective β1 drug. The average IOP reduction effect of timolol is 20%-30%, and it was considered the gold standard glaucoma drug therapy by the US Food and Drug Administration (FDA). Systemic adverse effect limited the use of BBs in some patients who have severe heart disease, asthma, or chronic obstructive pulmonary disease.

**Carbonic Anhydrase Inhibitors**

Carbonic anhydrase inhibitors (CAIs) reduce IOP by reducing the aqueous humor production. In the ciliary epithelium, the conversion of CO2 and H2O to HCO3– and H+ is an important process for aqueous humor production, and the conversion is catalysed by carbonic anhydrase isoenzyme II, the activity of which can be suppressed by CAIs. Both systemic and topical CAIs agents can be used to treat glaucoma. Systemic CAIs include acetazolamide and methazolamide. In the study of Dailey et al, acetazolamide (250 mg) produced a 21% decrease in IOP. Topical CAIs include dorzolamide and brinzolamide. Three times daily dorzolamide lowered IOP by 17% to 23%. Paraesthesias of hands and feet, nausea, vomiting, fatigue, and weight loss are common when using oral CAIs. For long-term users, renal stones may develop. Due to the
potential systemic complications, oral CAIs is usually reserved for short-term use only, such as before surgery. Although some local discomfort may happen such as burning, itching, topical CAIs are safe systemically.\textsuperscript{34}

**Alpha-agonists**

Alpha-agonists (AAs) have non-selective forms, which target both \(\alpha\)- and \(\beta\)-receptors, and selective forms, which target only \(\alpha\)-receptors.\textsuperscript{34} Non-selective AAs include epinephrine and dipivefrin, and they reduce IOP by increasing aqueous humor outflow via both the trabecular meshwork and uveoscleral pathways.\textsuperscript{39} Epinephrine reduced IOP by 15\% to 25\%.\textsuperscript{43} The systemic adverse events of non-selective AAs include headache, palpitations, high blood pressure, and anxiety.\textsuperscript{39} Selective AAs are divided into two subtypes: relatively selective \(\alpha_2\)-adrenoceptor agonistic with partially \(\alpha_1\)-adrenoceptor agonistic activity and relatively \(\alpha_2\)-adrenoceptor agonistic activity.\textsuperscript{39} The former one is clonidine (not commonly used) and the latter ones include apraclonidine and brimonidine. Apraclonidine (\(\alpha_2\)-adrenoceptor agonist) has been shown to reduce IOP by 20\% to 27\% via reducing aqueous humor formation and increasing outflow through the trabecular meshwork pathway.\textsuperscript{44, 45} By contrast, brimonidine has been shown to decrease IOP by approximately 24\% via reducing humor production and increasing outflow through uveoscleral pathway.\textsuperscript{46, 47} Also, brimonidine was found to reduce ganglion cell loss in an animal research model and slower rates of visual field progression independently to the IOP-lowering effect in an RCT.\textsuperscript{34} Both the studies suggested a potential neuroprotective effect of brimonidine.\textsuperscript{34} Because of the high rate of allergic blepharoconjunctivitis, apraclonidine is seldom used for long term.\textsuperscript{39} A notable systemic adverse event of brimonidine is central nervous system and respiratory suppression due to its significant blood-brain barrier cross ability.\textsuperscript{34} Therefore, it should be avoided in small children.\textsuperscript{39}

**Cholinergic agents**

Cholinergic agents can be divided into direct agonistic agents working directly on parasympathetic receptors in the eyes and indirect agonistic agents inhibiting acetylcholinesterase.\textsuperscript{39} Cholinergic agents reduce IOP by increasing aqueous humor outflow through the trabecular meshwork pathway.\textsuperscript{39} Pilocarpine is the most commonly used direct agonistic cholinergic agent. It directly stimulates the muscarinic receptors in
the ciliary muscle, widens the iridocorneal angle, and results in an increased outflow of aqueous humor through the trabecular meshwork.\textsuperscript{39} Pilocarpine can reduce IOP by 20% to 30%.\textsuperscript{48} Although with rare systemic adverse effects, the local adverse effects of pilocarpine are notable, such as diminished visual acuity due to pupillary constriction and accommodative spasm, brow ache, and rarely retinal detachment, and those adverse effects limit the use of pilocarpine.\textsuperscript{39} Echotothiophate iodide and demecarium bromide are the indirect cholinergic agents. The IOP reduction effect of echotothiophate is comparable to that of pilocarpine.\textsuperscript{49} Due to the potential prolong respiratory paralysis for general anesthesia patients and the cataractogenic effect, the indirect agents are not commonly used and restricted only to glaucomas in aphakia or pseudophakia.\textsuperscript{39, 50, 51}

**Fixed combinations**

According to the Ocular Hypertension Treatment Study, almost 50\% of POAG patients need two or more medications to achieve the target IOP level (IOP reduced by 20\% from baseline value with a final IOP less than 24 mmHg).\textsuperscript{14} Fixed combinations are ideal for those patients in terms of increasing patient adherence and persistence with therapy, owing to requiring fewer bottles, daily drop instillations, and maybe less cost.

- **Laser treatment**

**Argon laser trabeculoplasty**

In 1979, Wise and Witter initially demonstrated the IOP-lowering effect of argon laser trabeculoplasty (ALT).\textsuperscript{52} Shortly after its introduction, ALT has been playing an important role in the treatment of uncontrolled open-angle glaucoma for decades.\textsuperscript{53} In ALT, the argon green laser with 488 to 514 nm wavelength, is usually set at a 50-\(\mu\)m spot size, 0.1-second duration along with a 300 to 900-mW power, and targets on the adjunction between pigmented and non-pigmented trabecular meshwork.\textsuperscript{36}

**Mechanism of ALT**

The possible mechanisms of IOP-lowering effect after ALT include mechanical, biologic, and repopulation theory.\textsuperscript{54} Under the observation with light microscopy, ALT can cause crater formation of the trabecular meshwork and collagen whitening which indicates coagulative damage.\textsuperscript{55} Markedly fragmented trabecular meshwork along with disruption
of the lumen of Schlemm’s canal has been seen pathologically. Those changes may increase the outflow of aqueous humor. The biomechanical hypothesis suggests that the thermal energy after ALT simulates the cellular activity which causes IOP reduction. The cellular changes in the treated trabecular meshwork include recruitment of macrophages and increased release of cytokine, both of which can remodel the extracellular matrix followed by decreasing aqueous humor outflow resistance and hence reducing IOP. Repopulation theory suggests that after the damage of ALT, trabecular cells have the regenerative ability to maintain a porous and physiologically normal extracellular matrix barrier to the outflow of aqueous humor, and subsequently decrease IOP.

**Efficacy of ALT**

On average, ALT reduced baseline IOP by approximately 3.2 to 9.6 mmHg (reduced 12% to 35% from baseline IOP) at 1 year, 2.8 to 9.8 mmHg (11% to 36%) at 2 years, and 6.7 to 9.1 mmHg (29% to 34%) at 5 years. The documented IOP response after ALT varied substantially because of the heterogeneity of patient characteristics and laser setting. Time to 50% of eyes failure (median survival time) after ALT was approximately 2 years (success was defined as at least 20% or 3 mmHg IOP reduction without additional laser or surgical interventions).

**Adverse events of ALT**

In the Glaucoma Laser Trial, a transient IOP rise of greater than 5 mmHg and 10 mmHg were found in 34% eyes and 12% eyes respectively within 4 hours after 180-degree or 360-degree ALT. In that study, among the ALT treated eyes, 46% developed peripheral anterior synechiae during the 3-month follow-up. Mild iritis after ALT was reported in another study.

**Selective laser trabeculoplasty**

The introduction of selective laser trabeculoplasty (SLT) in 1995 provided a new choice for IOP reduction in eyes with OAG or ocular hypertension. The basic principle of SLT is using radiation energy from a 532-nm frequency-doubled Q-switched Nd:YAG laser with 400 μm spot size and duration of 3 nanoseconds which targets on the
pigmented trabecular meshwork. SLT selectively applied on the pigmented cells in trabecular meshwork without causing detectable collateral thermal damage.

**Mechanisms of SLT**

The mechanisms of SLT are not fully understood. In general, similar to ALT, SLT seems to increase the outflow via the trabecular meshwork pathway, resulting in IOP reduction. Findings in the experimental SLT-treated eyes included morphological changes in cellular level and biological processes. The morphological changes included disruption of trabecular endothelial cells, junction disassembly of Schlemm’s canal cells, etc. Besides, a series of biological changes in the anterior segments were identified after SLT, such as cytokine secretion, matrix metalloproteinase induction, and monocyte migration to the trabecular meshwork.

**Efficacy of SLT**

From the systematic review of Wong et al., the mean IOP reduction after SLT varied approximately from 1.4 to 12.0 mmHg, 1.8 to 9.1 mmHg, and 7.4 to 7.9 mmHg at post-laser 1 year, 2 years and 5 years respectively. Accordingly, the percentage of IOP lowering from baseline was 7% to 36%, 8% to 35%, and 32% to 33% at those tree time points depending on the difference of baseline IOP, type of glaucoma, and degree of SLT treatment, etc. Approximately, the median survival time (time of success in 50% eyes) was in post-laser 2 years if success was defined as at least 20% or 3 mmHg IOP lowering without additional laser or surgical interventions.

**Adverse events of SLT**

The adverse events after SLT are mild and rare. Although some discomforts may occur, such as redness, pain, and photophobia, they resolve spontaneously within a few days. A transient IOP rise (IOP spike) may happen in 0% to 28% treated eyes with $\geq$5 mmHg increase and in up to 5.5% treated eyes with $\geq$10 mmHg increase. It usually resolves within 24 hours with or without glaucoma medication. Peripheral anterior synechiae (scarring in the angle) occurred following SLT in 0% to 2.85% eyes according to 9 previous studies. Some isolated case reports of rare adverse events include the occurrence of hyphema, bilateral anterior uveitis, and choroidal effusion.
**Other types of laser trabeculoplasty**

**Micropulse diode laser trabeculoplasty** uses an 810-nm diode laser to produce micropulse emission of laser energy and to create sublethal thermal damage to the cells in the trabecular meshwork.**36** **Titanium sapphire laser trabeculoplasty** uses a 790-nm laser which emits flashlamp-pumped, near-infrared energy in pulses which last 5-10μs.**36** The efficacy and safety of those new technics need further evaluations.

- **Glaucoma surgery**

Glaucoma surgery is often conducted when target IOP is not achieved using medical and/or laser treatment.**3** Incisional glaucoma surgery for the treatment of open-angle glaucoma includes filtering surgery and glaucoma drainage-device surgery. The principle of the lowering IOP effect of glaucoma surgery is to open the current aqueous humor pathways or to create a new pathway to increase aqueous humor outflow.**27** Trabeculectomy is the most common filtering surgery. One study reported a maintenance of IOP below 21 mmHg in 57% patients without additional medication 20 years after trabeculectomy.**76** Complications after trabeculectomy include infection, suprachoroidal haemorrhage and low IOP, along with risk of endophthalmitis, and some of them can lead to visual impairment.**2** Clinical failure of the glaucoma drainage devices was estimated to occur at a rate of about 10% per year.**77** In the Tube Versus Trabeculectomy Study, the overall incidence of postoperative 1-month complications, notably wound leak and hyphema, was higher after the trabeculectomy with mitomycin C (incidence of early complications, 37%) than after the tube shunt surgery, a type of the drainage-device surgery, (incidence of early complications, 21%).**78**

**SLT versus other glaucoma therapies**

- **SLT versus medication**

Several randomised trials have concluded that the IOP-lowering effect did not differ between SLT and glaucoma medications. The study conducted by Nagar et al. showed that 360-degree SLT did not show a significantly different IOP-lowering effect compared with 0.005% latanoprost.**79** Another two RCTs compared SLT with topical antiglaucoma drugs, including beta-blockers, brimonidine, pilocarpine, dorzolamide, and latanoprost as monotherapy or in combination, and found similar IOP reduction between the two
In terms of treatment compliance, it has been well documented that poor adherence is common for glaucoma medication users.82

- **SLT versus ALT**

Regarding efficacy of IOP control, no significant difference was found between ALT and SLT in several systematic reviews and meta-analyses.70 83 84 The meta-analysis of Wang et al. found SLT produced a higher IOP reduction compared with ALT (weighted mean difference, 0.6 mmHg; 95% CI, 0.06 to 1.14 mmHg; p = 0.03).85 Peripheral anterior synechiae, which is a laser-related adverse event, have been shown to happen in 12% to 47% patients after ALT while in less than 2.8% patients after SLT.70 In terms of skill requirement, compared with SLT, the spot size of ALT is small, and the procedure requires more precise targeting and focusing. Therefore, SLT is easier for general ophthalmologists.

- **SLT versus surgery**

According to the RiGOR research, a prospective observational study, the proportion of patients, who achieved a 15% IOP reduction in 12 months, was higher in the surgery group (trabeculectomy, drainage device procedures, canaloplasty, Trabectome®, cyclophotocoagulation or nonpenetrating glaucoma procedures) than the ALT/SLT group (87% vs 57%).86

**Secondary open-angle glaucoma**

- **Pseudoexfoliative Glaucoma**

Pseudoexfoliative syndrome (PXF) is the most commonly identifiable cause of secondary open-angle glaucoma.87 PXF can convert to either angle-closure or open-angle glaucoma (pseudoexfoliative glaucoma, PXG) accompanied with the observation of the deposits of abnormal fibrillar extracellular white material on almost all the anterior structures of the eye.88 The white material is a major risk factor for both the development and progression of glaucoma.12 89 The clinical management of PXG is considered to be more difficult than POAG partially owing to a higher IOP level, a greater IOP fluctuation, and a higher incidence of IOP spike in PXG patients.90 However, patients with PXG have a comparable prognosis with POAG after SLT or ALT.91 92
• **Pigmentary glaucoma**

Pigmentary glaucoma is led by pigment dispersion syndrome (PDS). The typical characters of pigmentary glaucoma include vertical pigment accumulated on the back of the cornea (Krukenberg spindle), radial spoke-like transillumination defects in the mid-peripheral iris, and trabecular meshwork pigmentation. The current understanding of the IOP elevation is that the overloaded trabecular meshwork endothelial cells die after they phagocytose the pigment granules, and the loss of the endothelial cells causes the collapse of the trabecular beams resulting in the obstruction of the aqueous humor outflow and the following IOP increase. Pilocarpine is thought to be the most ideal therapy for pigmentary glaucoma because it can reduce the friction between the iris and lens zonules. However, because of some apparent side effects of pilocarpine, other types of glaucoma agents were also applied to pigmentary glaucoma. The success rate after SLT on pigmentary glaucoma patients did not differ from other types of open-angle glaucoma, but it is necessary to reduce laser energy for those with severe pigmented angles. Specifically, several studies have shown ALT was effective particularly in pigmentary glaucoma. Compared with POAG patients, a higher rate of incisional surgery was reported in pigmentary patients to attain a satisfactory IOP control.

• **Ocular hypertension**

According to the definition from the Guideline Development Group (GDG) in England, ocular hypertension (OHT) is a condition of eyes characterized as IOP > 21 mmHg, open drainage angles observed on gonioscopy without glaucomatous optic disc damage, detectable nerve fibre layer defect, or visual field loss. In addition, the elevated IOP cannot be explained by other causes, such as trauma or uveitis. OHT can accompany with pigment dispersion or pseudo-exfoliation. OHT patients are also considered glaucoma suspects. The Ocular Hypertension Treatment Study reported that at 60-month follow-up, the cumulative probability of development of POAG was 4.4% in the patients treated with glaucoma medications and 9.5% in the patients without treatments (hazard ratio, 0.4; 95% CI, 0.27 to 0.59; p<0.001). Treatment was recommended to initiate for high-risk ocular hypertension patients based on IOP and central corneal thickness (CCT).
Although the GDG guideline suggested the first line treatment was prostaglandin analogues (PGAs) or beta-blockers (BBs), some authors found that SLT as the first line treatment for OHT not only had a comparable efficacy in lowering IOP with PGAs but also had an advantage of medical adherence and reduced side effects from glaucoma medicine.\textsuperscript{82, 96}

1.2 Rationale of the study

The same with ALT, the efficacy of SLT in IOP reduction may diminish over time.\textsuperscript{58, 60} After SLT, treatment success (an IOP reduces at least 20\% from baseline score) was recorded in 66.7\%-75\% eyes at 6 months, 58\%-94\% at 12 months, and 11.1\%-31\% at 5 years.\textsuperscript{69} This implies that for the medically uncontrolled patients, up to approximately 90\% of those may need a repeated laser within 5 years after the first SLT to avoid or postpone the time for an incisional glaucoma surgery, which may cause more complications than laser treatments.

Except for few crack-like defects of the beams of the trabecular meshwork, the SLT-targeted tissue has been found intact.\textsuperscript{55} It provides the theoretical possibility that SLT is repeatable. Several studies have demonstrated a comparable effect of IOP reduction between initial SLT and repeat SLT no matter after initial 180 or 360-degree trabecular meshwork treatment.\textsuperscript{98, 99, 100, 101, 102, 103, 104} However, most of the studies have noticeably methodological limitations. In addition, how many sessions SLT can be repeated has not been evaluated.

Argon laser trabeculoplasty is the first type of laser trabeculoplasty and has been found successful in reducing IOP based on level I evidence, which is the highest level of the rating scale of evidence-based medicine developed by the Oxford Centre.\textsuperscript{105} Particularly, an RCT comparing ALT and glaucoma medication for the newly diagnosed POAG patients showed mean IOP reduction was approximately 9 mmHg for the ALT group and 7 mmHg for the medication group at 1 year.\textsuperscript{106} Therefore, ALT was selected as the reference laser treatment.

Three RCTs have shown that the primary SLT and ALT have a comparable IOP-lowering
The choice of equivalence study design was based on the hypothesis that the equivalent efficacy of SLT and ALT also holds for previous SLT-treated patients and the facts that some features of SLT make it outweighs ALT, such as less peripheral anterior synechiae and simpler operation skill.

1.3 Goal and objectives

The goal of the study was to evaluate whether SLT is repeatable and if so whether SLT and ALT have an equivalent efficacy after the failure of the initial SLT.

**Primary objective:**

Currently, IOP is the only modifiable causative factor for glaucoma. Furthermore, the aim of either SLT or ALT is to reduce IOP. Therefore, the primary objective of the study was to test whether SLT has an equivalent IOP reduction effect from baseline to 12 months compared with ALT. To generalize the study outcome, data from POAG, PXF, PDS, OHT patients were included.

**Secondary objectives:**

- To compare the efficacy and safety of SLT and ALT at multiple follow-up time points.

- As described in Section 1.1, approximately 50% patients failed to reach a 20% or 3-mmHg IOP reduction at 2 years after either SLT or ALT. It indicates individuals have various response to the laser treatment. Many studies have identified baseline IOP as the positive predictor for laser treatment success. However, the outcomes of the predictive ability of some other predictors are controversial. Hence, it is necessary to explore the predictors of treatment success after laser trabeculoplasty as one of the secondary objectives in this thesis.

1.4 Data resources and role of the author

To answer the research questions, data were obtained from an ongoing multicentre RCT, which is an equivalence study design. The trial was registered in ClinicalTrials.gov on September 11, 2012 (registry number: NCT01687465) with a title of “A randomized
clinical trial of selective laser trabeculoplasty (SLT) in open-angle glaucoma who had been previously treated with complete SLT” and an acronym of “Repeat Laser Study”. Patients with POAG, PXF, PDS, and OHT who had received 360-degree SLT were recruited. Because of uncontrolled IOP with medicine and previous SLT, they had been scheduled laser treatment and were randomly allocated to receive either SLT or ALT. The length of the follow-up time after the laser treatment is 12 months. My role is to analyse the data from this ongoing RCT without involving in any study design or site work of this RCT.

1.5 Contents of each chapter

There are five chapters in this thesis, including the introduction in Chapter 1. Chapter 2 contains the literature review and summarises studies comparing SLT and ALT with an RCT design, evaluating repeat SLT, and exploring factors predicting the success of laser trabeculoplasty. Chapter 3 describes the data characteristics and the analysis methods. Chapter 4 provides the results of the data analyses. Chapter 5 interprets the study outcomes, analyses the strengths and limitations of the thesis, makes a conclusion of the thesis work, and proposes future studies about repeat SLT treatment.
Chapter 2 Literature Review

There are four sections in this chapter. Section 2.1 summarises the randomised controlled trials comparing selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT). Studies about repeated SLT are reviewed in Section 2.2. Section 2.3 describes the predictors of laser trabeculoplasty efficacy evaluated in previous studies. A summary of this chapter is provided in Section 2.4.

2.1 RCTs comparing SLT and ALT

Several randomised clinical trials have been published to compare the efficacy and safety between SLT and ALT in the last a decade or so. These are RCTs that look at first laser use, but not repeatability.

Damji et al.\textsuperscript{109} presented an RCT comparing IOP-lowering effect between SLT and ALT with 6-month follow-up. Patients were treated with either standard 180-degree SLT or 180-degree ALT. Eighteen eyes were treated in each group. Diagnoses included POAG, PXF, PDS, OAG status post peripheral laser iridotomy, and Aphakic glaucoma for 19, 10, 3, 3, and 1 eye respectively. The authors found during the observation period, the two groups had a comparable IOP reduction effect, with a mean $\pm$ SD of 4.8 $\pm$ 3.4 mmHg in the SLT group and 4.7 $\pm$ 3.3 mmHg in the ALT group. Furthermore, in the patients with previously failed ALT treatment, SLT (7 eyes) showed a better outcome in the reduction of IOP than ALT (8 eyes) (6.8 $\pm$ 2.4 mmHg versus 3.6 $\pm$ 1.8 mmHg, $p = 0.01$).

In another RCT also conducted by Damji et al.\textsuperscript{61} with 1-year follow-up, more patients were recruited. There were 176 eyes from 152 patients enrolled in the study, with 102 having POAG, 52 of PXF, 12 of PDS, 4 of combined mechanisms, and 5 with other diagnoses. The surgical parameters were the same as those published in 1999. Both the mean $\pm$ SD IOP reduction (5.86 $\pm$ 6.15 mmHg versus 6.04 $\pm$ 4.82 mmHg) and Kaplan–Meier survival analysis in laser success were not significantly different between the SLT group (73 eyes) and the ALT group (74 eyes). Among the SLT subgroup, those eyes
treated previously with 360-degree ALT had a significantly greater mean IOP-lowering effect (7.1 mmHg) than those treated with 180-degree ALT (4.8 mmHg), or those without previous ALT treatment (5.7 mmHg). In the ALT group, the eyes which had a previous 180-degree ALT treatment showed a significantly greater mean IOP reduction (7.0 mmHg) than those had a previous 360-degree ALT treatment (4.5 mmHg) or no treatment (6.0 mmHg). In the eyes diagnosed as PXF, mean IOP was reduced by 5.7 mmHg in the SLT group (n=16) and by 5.4 mmHg in the ALT group (n=23), which had a similar outcome with the overall group.

Later, the same research group\textsuperscript{60} reported a series of follow-up outcomes from the previous patient cohort up to 5 years. The follow-up was completed for 150 eyes at 2 years, 142 eyes at 3 years, 134 eyes at 4 years, and 120 eyes at 5 years. The numbers of eyes in each group at any time point were not significantly different. The results showed that there was no significant difference between the SLT and ALT group regarding IOP reduction from baseline to 2, 3, 4, or 5-year follow-up time point. Also, the surgical success rate was comparable between the two groups during the 5-year observation period. IOP decreased by $7.4 \pm 7.3$ mmHg (mean $\pm$ SD) in the SLT group (n=64) and $6.7 \pm 6.6$ mmHg in the ALT group (n=56) at 5-year post-laser check-up.

Martinez-de-la-Casa et al\textsuperscript{110} reported an RCT comparing the efficacy of IOP reduction between the 180-degree SLT and 180-degree ALT. All the patients were open-angle glaucoma (OAG) without PXF or PDS and were poorly medically controlled with IOP $>21$ mmHg. Both of the treatment groups included 20 eyes from 20 patients. At 6-month post-treatment visit, the mean percentage IOP decreased by 22.2\% in the SLT group and 19.5\% in the ALT group (p = 0.741). Absolute IOP reduction value was not reported in the study.

Best et al.\textsuperscript{111} conducted an RCT using two different laser systems (Otello and Selecta II) for the 360-degree SLT treatment to compare the IOP reduction effect with the 360-degree ALT treatment for OHT or OAG patients. In total, two-year follow-up data were available for 106 eyes in the Otello SLT group, 110 eyes in the Selecta SLT group, and 32 eyes in the ALT group. The mean IOP reduction for those three groups was 1.7 mmHg, 1.8
mmHg, and 2.1 mmHg respectively at the 1-year follow-up, and it was 1.7 mmHg, 1.7 mmHg, and 2.0 mmHg respectively at the 2-year follow-up. However, the authors did not report the statistical comparison of the difference among the three groups.\textsuperscript{83}

Birt et al.\textsuperscript{62} reported an RCT in 2007. All the patients had a diagnosis of POAG, PXF, or PDS. Twenty-seven patients who were given 360-degree ALT previously were assigned to 180-degree SLT treatment directly. The rest of the participants without SLT or ALT treatment history were randomly assigned to 180-degree SLT treatment group (n = 30) or 180-degree ALT treatment group (n = 39). Mean percentage of IOP reduction was significant at 1 year for all the three groups with 23.0\% (SD 3.8\%) in the SLT group, 19.3\% (SD 4.5\%) in the SLT after ALT group, and 24.1\% (SD 2.5\%) in the ALT group respectively. The difference among the groups was not significant. Furthermore, the study showed that the number of medication used at one year significantly reduced in both the SLT only group and the SLT after ALT group, but not in the ALT only group. Absolute IOP reduction values were not provided in the paper.

Russo et al.\textsuperscript{112} performed an RCT comparing the IOP reduction effect between the 360-degree SLT and the 360-degree ALT on POAG patients. A total of 120 eyes of 120 patients were recruited with 60 eyes in each group. After the initial treatment, 36 patients with IOP > 20 mmHg at 3 months after the laser treatments were retreated randomly with another 360-degree SLT or 360-degree ALT and included as Group B. The rest of the patients were included in Group A. In Group A, there were 43 eyes underwent SLT and 41 eyes underwent ALT. The mean IOP reduction at 12 months was 6.01 mmHg in the SLT group and 6.12 mmHg in the ALT group (p = 0.794). No significant difference was found between the two treatment groups. In Group B, at 12-month follow-up, patients treated with repeat SLT showed a significant difference of mean IOP reduction compared with repeat ALT (6.24 mmHg versus 4.65 mmHg, p < 0.01). The results suggested that SLT was more effective than ALT regarding IOP reduction in patients with previous laser history. However, the initial and secondary SLT or ALT allocation can lead to four combinations, namely repeat SLT after ALT or SLT and repeat ALT after ALT or SLT. Therefore, the outcome of the comparison of the efficacy between repeat SLT and repeat ALT can be confounded by the type of the previous laser.
Liu et al reported an RCT in comparison of SLT and ALT with final IOP among patients who were 60 or less. One eye from 42 patients was randomised to receive 180-degree SLT (20 eyes) or 180-degree ALT treatment (22 eyes). All the patients were not treated with any laser trabeculoplasty before randomisation. The glaucoma type included POAG (19), juvenile open-angle glaucoma (10), OHT (8), PXF (2), mixed mechanism glaucoma (1), low-tension glaucoma (1), and PDS (1). At 1-year follow-up, the mean ± SD post-laser IOP was 15.4 ± 3.9mmHg in the SLT group and 19.2 ± 4.9mmHg in the ALT group with a significant difference (p=0.03). At 2-year follow-up, the mean ± SD post-laser IOP was 17.3 ± 3.7mmHg and 19.1 ± 5.7mmHg in the SLT and ALT group respectively without significant difference (p>0.05). The mean IOP reduction was 3.7 and 1.8 mmHg in the first and second year after SLT, and it was 2.7 and 2.8 mmHg in the first and second year after ALT. IOP increased in the second year in the SLT group was considered that the effect of SLT diminished with time.

Rosenfeld et al. conducted an RCT comparing the IOP-lowering effect of SLT with ALT targeting only pseudophakic patients (patients with previous cataract surgery). Fifty-two eyes from 52 patients with POAG, OHT, PXF, or PDS were randomly allocated to either the 180-degree SLT or 180-degree ALT treatment group. Those patients who needed to either modify the type or number of the IOP-lowering medicine, undergo a trabeculectomy, or repeat ALT treatment were excluded from the analyses. It led to 19 eyes in the SLT group and 18 eyes in the ALT groups included in the final analyses. In those 37 patients, the baseline IOP was comparable between the two groups. At the 12-month check-up, the mean IOP reduction was 4.3 mmHg and 3.23 mmHg in the SLT and ALT group respectively without a significant difference (p = 0.269). This study generalized the comparison of efficacy between SLT and ALT to previous cataract surgery patients and used the single eye per patient in the analyses. However, the sample size is relatively small.

Popiela et al. studied the IOP-lowering effect of 180-degree SLT in comparison with 180-degree ALT. Patients who had OAG with deteriorated visual field under maximal tolerated medical therapy were recruited. In total, 27 patients were included with 21 diagnosed as POAG, 3 normal pressure glaucoma, 1 PDS, 1 PXF, and 1 juvenile
One eye of each participant was randomly selected to receive SLT treatment and the other one received ALT treatment. At the final check-up (post-laser 3 months), the mean ± SD IOP reduction from baseline was 2.58 ± 4.62 mmHg in the SLT group and 2.63 ± 3.6 mmHg in the ALT group, and the difference between the two groups was not significant (p = 0.84).\textsuperscript{83}

Kent et al.\textsuperscript{115} reported a multicentre RCT comparing SLT and ALT in the efficacy of IOP reduction in PXF patients. In total, 76 eyes from 60 patients were recruited from 5 Canadian academic hospitals. Eyes were randomly allocated to either 180-degree SLT treatment group (31 eyes) or 180-degree ALT treatment group (45 eyes). Data at 6 months was available in 63 eyes. At 6-month follow-up, the IOP reduced by 6.8 ± 5.4 mmHg (mean ± SD) in the SLT group and 7.7 ± 7.12 mmHg in the ALT group with a non-significant difference (p = 0.56).

Wang et al.\textsuperscript{84} synthesized the results from 6 RCTs\textsuperscript{58,60,113,110,62,115} comparing SLT and ALT in OAG patients with meta-analysis. The types of OAG included POAG, PXF, and mixed. Patients were treated with either 180-degree SLT or 180-degree ALT. The pooled result of 4 studies showed the difference of IOP reduction between the two treatments was significant at post-treatment 3 months. It favoured SLT with a weighted mean difference (WMD) of 1.19 mmHg (95% CI 0.41 to 1.97 mmHg, $I^2 = 0\%$, p=0.003). The two treatments were identical at 1 hour, 1 week, 1 month, 6 months, and 1 year in terms of IOP reduction according to the pooled results of the 6 studies. Furthermore, the author conducted a subgroup analysis for patients who were naïve to laser. In this subgroup, the author did not find a significant difference between SLT and ALT at 1 year based on 3 studies. Similarly, in the subgroup for patients who had previously received either SLT or ALT treatment, the IOP reduction at 6 months was comparable between the two treatments with a WMD of 1.92 mmHg (95% CI -0.91 to 4.74 mmHg, $I^2 = 77.3\%$, p=0.18). In addition, the pooled result from four studies showed SLT reduced more glaucoma medication use than ALT by 0.57 mmHg (95% CI 0.00 to 1.14; p=0.05). The success rate of SLT versus ALT was not significantly different with RR = 1.03 (95% CI 0.83 to 1.28) from 3 studies with various definitions of success. Two studies reported the anterior inflammation after laser, the results were contradicted and lacked a uniform
standard of inflammation measurement. One study analysed the incidence of IOP spike and did not find a difference between the two treatments.

Wong et al.\textsuperscript{70} did another meta-analysis including 4 RCTs\textsuperscript{58} \textsuperscript{60} \textsuperscript{113} \textsuperscript{115} to compare SLT with ALT. The difference of absolute IOP reduction at 6 months to 5 years in pooled mean was 0.5 mmHg (95\% CI, -1.5 to 0.4 mmHg) comparing SLT and ALT with fixed effect model ($I^2 = 0$). Similarly, the treatment success rate was comparable between SLT and ALT (OR = 1.2; 95\% CI, 0.7 to 1.8). In terms of reducing number of glaucoma medication, the pooled difference between SLT and ALT was 0.2 (95\% CI, 0.5 to -0.08) from two RCTs.\textsuperscript{58} \textsuperscript{60}

Wang et al.\textsuperscript{85} reported a systematic review and meta-analysis synthesizing the information from 6 RCTs.\textsuperscript{58} \textsuperscript{116} \textsuperscript{61} \textsuperscript{110} \textsuperscript{62} \textsuperscript{112} The primary outcome was IOP reduction from baseline to post-treatment 6 to 24 months. The difference in IOP reduction of SLT versus ALT was significant with a WMD of 0.60 mmHg (95\% CI, 0.06 to 1.14 mmHg; $p = 0.03$) and an $I^2$ of 31\%. One of the secondary outcomes was therapeutic IOP response, which was defined as IOP-lowering $\geq$ 3 mmHg and/or $>$ 20\% from baseline. The relative risk (RR) of therapeutic IOP response was comparable with the two lasers, which was 0.84 (95\% CI, 0.61 to 1.38; $p = 0.05$). One of the limitations of this review is the information bias. First, it included the study of Júnior et al. as an RCT, but the study was reported as a prospective, nonrandomised interventional study.\textsuperscript{116} Second, the author stated that the patients in Group B was naïve to laser from the study of Russo et al., and it is not correct since those patients were described as having either SLT or ALT treatment previously in the literature.\textsuperscript{112} Furthermore, using the data from the Group B to run a meta-analysis should be cautious because the outcomes may be biased owing to the variation of type of the initial laser treatment.

In summary, SLT showed a comparable efficacy with ALT regarding IOP reduction for OAG patients in a number of the RCTs and three meta-analyses. The subgroup analyses showed SLT might superior to ALT in patients who had received either SLT or ALT laser treatment before.\textsuperscript{109} \textsuperscript{113} However, because of the imperfect study design and the small sample size in those subgroup analyses, further investigations are needed.
2.2 Repeat SLT

Some noticeable structural changes of the trabecular meshwork after the application of ALT have been observed pathologically. The typical change was crater formation surrounded by coagulative damages. Some authors have described a markedly decreased efficacy of the repeat ALT compared with the primary ALT. Those outcomes suggest that structural changes of the trabecular meshwork caused by ALT can lower the efficacy of the next ALT.

By contrast, SLT does not cause scarring or contraction of the targeted tissue. Theoretically, it allows the treatment to be repeated. Several studies have evaluated the efficacy and safety between the primary and repeat SLT.

Hong et al. reported the efficacy of repeat SLT after the failure of the initial 360-degree SLT treatment. The author conducted a retrospective chart review, which included 44 eyes of 35 patients with POAG, PXF, or PDS. Those patients had the IOP controlled successfully for at least 6 months after the first 360-degree SLT treatment and received a second 360-degree SLT treatment (102 shots on average). Twenty eyes repeated the SLT at 6 to 12 months after the first one, and 24 eyes repeated the treatment at equal or over 12 months after the initial one. The IOP reduction was significantly greater for the first SLT than the second one during the 1 to 3-month follow-up, with an average value of 5 mmHg for the SLT1 and 2.9 mmHg for the SLT2 ($p = 0.01$). However, the IOP-lowering effect within 5 to 8 months after the SLT treatment was not significantly different between SLT1 and SLT2 (mean IOP reduction, $-4$ mmHg vs $-2.9$ mmHg). The authors also compared the early repeated (6-12 months) and the late repeated ($\geq 12$ months) SLT treatment effect and found no significant difference of IOP change during 1 to 4-week, 1 to 3-month, 5 to 8-month, or 15 to 21-month follow-up. Also, no uveitis was documented in the second SLT. IOP spike was observed in one eye after both the first and the second SLT. The limitation of this study includes baseline IOP being measured three times before the first SLT but being measured only one time before the second one. The single examination of baseline IOP before the second SLT may introduce measurement bias.
Avery et al.\textsuperscript{100} conducted another retrospective chart review evaluating the efficacy of repeat SLT. The study included 42 eyes from 42 patients who had POAG and excluded those with PXF or PDS. Nine of the 42 eyes received a third SLT treatment. All the three procedures were performed on 360-degree trabecular meshwork with 40-50 shots. On average, IOP decreased by $3.6 \pm 4.8$ mmHg (SD), $4.5 \pm 4.5$ mmHg, and $3.6 \pm 2.9$ mmHg at 3 to 4 months after the first, second, and third SLT treatment respectively. No significant difference was found between the first and the second treatment. In terms of duration of success, the author compared the first and the second SLT treatment in 28 eyes, and found the median survival time was 3 months for the first SLT versus 11 months for the second SLT (hazard ratio = 0.43; 95% CI, 0.27 to 0.69; p < 0.01). It suggested that the effect of repeat SLT treatment for POAG patients may last longer than that of the initial treatment. Some limitations of this research should be considered. First, the sample size is relatively small and makes the outcome of survival analysis less accurate. Second, how the baseline IOP was measured and the comparison of complication between the first and the second SLT treatments were not reported.

Khouri et al.\textsuperscript{99} retrospectively reviewed the electronic medical records from 45 eyes of 25 subjects, who underwent two 360-degree SLT treatments. The mean ± SD interval between the first and the second SLT was $27 \pm 12$ months. The follow-up time was up to 24 months. The baseline IOP was comparable for the two SLT treatments. The mean ± SD of IOP change peaked at 4 months ($4.6 \pm 2.5$ mmHg for the first SLT and $3.9 \pm 6.3$ mmHg for the second SLT) and reached the lowest at 24 months ($2.8 \pm 3.4$ mmHg for the first SLT and $2.7 \pm 5.5$ mmHg for the second SLT) in both the two SLT treatments. At 12 months, the mean ± SD IOP reduction was $3.8 \pm 3.5$ mmHg and $2.9 \pm 5.8$ mmHg after the first and the second SLT treatment. Except at 4, 8, and 12 months, where the initial SLT yielded a significantly greater IOP reduction than the repeated one, the effect was identical at 1, 18, and 24 months. At 24 months, 8 of 28 (29%) and 11 of 28 (39%) versus 10 of 28 (36%) and 15 of 28 (54%) of eyes achieved an IOP reduction ≥20% and ≥15% after the second versus the first SLT (p > 0.05). No IOP spike was observed in either SLT treatment. The study had the advantage of baseline IOP measurement methods being the same for the two SLT treatments. One of the limitations is that two eyes of
some patients were included in the analyses. Treating the two eyes in one person as independent subjects and ignoring the correlation between the two eyes may falsely produce a precise confidence interval and a small p value (increase type I error). \textsuperscript{119, 120}

Ayala et al.\textsuperscript{98} reported a prospective RCT for evaluating the IOP-lowering effect of repeat SLT. Patients who had previous inferior 180-degree SLT and needed to receive a second SLT were recruited. Each patient was randomly allocated to receive another 180-degree SLT either at the same trabecular meshwork area or the untreated trabecular meshwork area. The average time interval between two SLT treatments was 12.9 months. The patients were diagnosed as POAG or PXF. A total of 80 eyes from 80 patients (40 eyes in each group) were included in the analyses. No loss-to-follow-up was documented. IOP reduction at post-laser 2h, 1, 3, or 6 months were not significantly different between the primary and repeat SLT groups (ANOVA, p=0.137). At 1 month, the mean IOP reduction was 5 mmHg in both groups. The authors did not report the scale of IOP change at the other time points. Anterior chamber inflammation was similar for each group, and no IOP spike (an IOP goes up > 6 mmHg from baseline) was detected at each check-up. Noticeably, PXF was diagnosed in 62.5% of all the patients.

Polat et al.\textsuperscript{121} conducted a retrospective chart review to explore the IOP-lowering effect of repeated 360-degree SLT. There were 38 eyes of 38 participants who were diagnosed as POAG, PXF, or PDS in the study. The mean IOP reduction at each time point throughout the 24-month follow-up ranged from 2.9 to 5.7 mmHg for the initial SLT and 2.3 to 4.4 mmHg for the repeat SLT without significant difference between the two SLTs. Kaplan-Meier survival analysis showed the median survival time was 19 months and 35 months for the first and second SLT, respectively if success is defined as no addition IOP-lowering medications, laser treatments, or incisional glaucoma surgeries. In addition, the median duration of IOP lowering ≥ 20% from baseline was 9 months for the first SLT and 12 months for the second SLT. No IOP spike nor severe inflammation was noticed for both SLTs. One of the advantages of this study is that only one eye per patient was included in the analyses. It can avoid the consideration of cluster effect in the outcome analyses.
Durr et al.\textsuperscript{103} reported a retrospective chart review evaluating the effect of 360-degree SLT on IOP control. Thirty-eight independent eyes who had POAG, normal tension glaucoma, or PXF were included in the study. Five patients were lost to follow-up after the first SLT, and another 5 patients were lost to follow-up after the second SLT during the 15-month study period. IOP reduced 1.8 $\pm$ 3.2 mmHg (mean $\pm$ SD) and 2.2 $\pm$ 3.7 mmHg at 15 months after the first and the second SLT, respectively. No significant difference was found during the 1, 6, and 15-month post-laser treatment time point comparing the two SLTs in IOP-lowering magnitude with ANOVA analysis (p=0.53).

In summary, according to the available information, repeat SLT is comparable to primary SLT regarding IOP reduction. Either IOP spike or post-laser inflammation is rare. However, only one study is an RCT design, and the others are all retrospective chart review. The sample size of most of the previous studies is moderate. Therefore, more studies with better study design for evaluating the efficacy of repeat SLT are needed.

To our best knowledge, no research has been reported comparing SLT and ALT after the initial SLT treatment.

### 2.3 Predictors of the IOP-lowering effect of laser trabeculoplasty

#### Baseline IOP

Higher baseline IOP or pre-laser IOP was found to significantly predict better outcomes after ALT or SLT in a large number of studies. The positive correlation was identified both in IOP reduction or treatment success with univariate as well as multivariate analysis.\textsuperscript{122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137} In contrast, Odberg et al. and Elsås et al. found higher baseline IOP to be a significant predictor for ALT treatment failure.\textsuperscript{138 139}

#### SLT Success of fellow eye

Regarding the correlation of two eyes in SLT response, Lee et al.\textsuperscript{140} performed a prospective cohort study evaluating the correlation of IOP between paired eyes after bilateral SLT. Both eyes of 42 patients with POAG or normal tension glaucoma. The IOP
reduction was highly correlated between the paired eyes at post-laser 1 day, 1 week, and 1 month (Spearman r = 0.7 to 0.9; p < 0.0001). Among those patients, 42.9% had bilateral success and 38.1% had bilateral non-success. The rest of the paired eyes (19%) had a contradicted outcome. Similarly, the retrospective medical record review of Shazly et al. found that the percentage of IOP reduction for the first eye and the fellow eye was highly correlated. Among those patients, 42.9% had bilateral success and 38.1% had bilateral non-success. The rest of the paired eyes (19%) had a contradicted outcome. Similarly, the retrospective medical record review of Shazly et al. found that the percentage of IOP reduction for the first eye and the fellow eye was highly correlated. Aqueous humor dynamics

Recently, Gulati et al. were the first to evaluate the association between aqueous humor dynamics and SLT response. They found higher aqueous flow, lower outflow facility, and lower uvescleral outflow at baseline significantly predicted a greater IOP reduction after SLT. These variables are not easy to record clinically and are not part of typical clinical care.

Factors not correlated with the IOP-lowering effect of laser trabeculoplasty

Gender, race, spherical equivalent, lens status, anterior chamber angle grade, retinal nerve fibre layer thickness, type of glaucoma, glaucoma duration, some glaucoma risk factors (hypertension, myopia, family history of OAG), previous ALT, and washout of glaucoma eye drops have not been shown as the significant predictors for SLT or ALT success.

Specifically, Seymenoğlu et al. reviewed the history of patients who had either phakic or pseudophakic eye status (no previous cataract surgery vs previous uncomplicated cataract surgery with implantation of posterior chamber intraocular lens) and received 360° SLT. In total, 88 eyes from 88 patients were included. The outcome after SLT was comparable between phakic and pseudophakic eyes regarding absolute IOP reduction, laser success rate, and percentage IOP reduction up to 12-month follow-up.

Also, post-laser treatment medication (nonsteroidal anti-inflammatory drugs versus steroid) did not show a significant correlation with SLT success.
Contradicting predictors of the IOP-lowering effect of laser trabeculoplasty among different studies

Age
Age was found to have no predictive value for laser success in most of the studies. However, Ayala et al. found that older patients were more likely to fail earlier.

Diabetes
Both the studies of Koucheki et al. and Gracner et al. found non-diabetic patients had less IOP reduction or treatment success rate after SLT. By contrast, the correlation was not found in several other studies.

Maximum IOP
Mao et al. found maximum IOP was an independent predictor for SLT success with an adjusted OR of 0.9 (95% CI, 0.9 to 1.0; p = 0.0221), which meant higher maximum IOP tended to have a lower success rate. The result is contrary to that in the study of Martow et al., who found the highest ever recorded maximum IOP was not associated with SLT success.

Central corneal thickness
Shazly et al. conducted a retrospective chart review for consecutive patients who underwent SLT. The baseline IOP was comparable between the two groups of patients with different central corneal thickness (CCT). Using an independent sample t-test, the authors found that patients with central corneal thickness (CCT) <555 μm had a greater mean percentage of IOP reduction compared to those with CCT ≥ 555 μm during the 30-month follow-up period. However, the conclusion contradicts those from other studies, in which an association between CCT and SLT success was not found. Studies have shown that thinner central corneal thickness (CCT) independently predicted the development and progression of open-angle glaucoma. Those findings may suggest that CCT could indicate some biomechanical or historical characteristics of eyes. Therefore, it is reasonable to keep exploring the association between CCT and laser treatment effect in our study.
**Trabecular meshwork Pigmentation, Exfoliation**

In the study of Chen et al., trabecular meshwork pigmentation showed a positive effect of IOP reduction at post-SLT 7 months, and the interaction effect with exfoliation was also significant at this time point. The positive correlation between the scale of trabecular meshwork pigmentation and degree of IOP decrease after SLT was also found in the study of Wasyluk et al. This positive correlation was also identified after ALT treatment. Nonetheless, Gracner et al. found a negative correlation between the grade of trabecular meshwork pigmentation and successful SLT. Furthermore, other studies did not find a predictable effect of trabecular meshwork pigmentation on SLT success. It is known that pigmented cells in the trabecular meshwork have a greater optical absorbance to the laser than the adjacent cells, and this feature provides the possibility that SLT can selectively target on the pigmentation cells. Hence, the degree of pigmentation of trabecular meshwork is likely to be correlated with the effect of SLT. Furthermore, ALT was found particularly effective in pigmented glaucoma in several studies. Therefore, it is necessary to evaluate whether the degree of pigmentation of trabecular meshwork can predict the success of laser treatment in our study.

**Visual field**

Two studies found pretreatment visual field defect predicted ALT treatment failure. Odberg et al. found the stage of visual field defect (1 to 5 stages) predicted ALT treatment failure with RR = 2.1 (95% CI, 1.2 to 3.6; p = 0.01) with COX regression analysis. By contrast, visual field index was not found to be significantly associated with SLT treatment success in another two studies.

**Laser parameter**

Nagar et al. found success rate was greater for patients who received 180-degree or 360-degree SLT than those received 90-degree SLT. Higher energy level within 214.6 to 234.9 mJ was found to be associated with more IOP reduction after SLT. Similarly, Habib et al. and Ayala et al. found higher laser energy predicted a longer time to failure after the SLT treatment. However, regarding ALT treatment, Grayson et al. found a significantly longer time to failure with 50 burns on 180-degree trabecular meshwork compared to 100 burns on 360-degree trabecular meshwork, which suggested lower
energy for better outcomes. Many other studies, by contrast, did not find a significant correlation between laser parameters (location, the range of treated trabecular meshwork, the number of shot, or total laser energy) and treatment success.

Type of glaucoma medication

Prostaglandin analogues

Hirn et al. compared prostaglandin analogues (PGAs) naïve patients with PGAs users and found IOP reduction was significantly greater in the PGAs naïve group after the SLT treatment during the 1-year follow-up. A comparable conclusion was drawn from Bruen et al., stating that PGAs used at baseline was negatively associated with IOP-lowering effect after adjusting for baseline IOP. Compared to timolol/dorzolamide fixed combination users, PGAs users showed a less efficacy of SLT treatment in the study of Kara et al. Furthermore, Alvarado et al. suggested a positive PGAs response predicted both treatment success and IOP reduction magnitude after SLT, and those using PGAs at baseline had a poor SLT treatment outcome. While those studies demonstrated a negative association between PGAs and SLT treatment effect, Scherer et al. found patients using PGAs before and during the perioperative period had a greater absolute or percentage IOP reduction than those without using PGAs.

Carbonic anhydrase inhibitors

Woo et al. conducted a five-year retrospective study to explore the correlation between the IOP-lowering medications and SLT response. In total, 206 eyes from 206 patients with POAG, PDS, PXF, or OHT were included in the study. Among the 206 patients, 55 completed the five-year follow-up. The result showed systemic or topical carbonic anhydrase inhibitors (CAIs) were significantly associated with a higher risk of failure during 60 months after a primary SLT (hazard ratio = 1.852; 95% CI, 1.175 to 2.919; p = 0.008). By contrast, Lee et al. found a positive independent association between topical CAIs and SLT success at 1 month for POAG and normal tension glaucoma patients (OR = 18.63; 95% CI, 2.92 to 140.07; p = 0.002).
A number of other studies did not find a predictive effect of the type of glaucoma medication regarding SLT or ALT efficacy.\textsuperscript{122 123 126 132 135 137 147 148 162}

**Number of glaucoma medication**

Lee et al. found using three types of IOP-lowering medications at baseline was negatively associated with SLT success in either univariate (OR = 0.34; 95% CI, 0.11 to 0.94; $p = 0.037$) or multivariate regression (OR = 0.02; 95% CI, 0.00 to 0.32; $p = 0.0081$) analysis.\textsuperscript{158} However, other studies did not find such a significant association.\textsuperscript{122 123 132}

### 2.4 Summary

Previous RCTs comparing SLT and ALT agreed with each other and concluded that SLT was comparable to ALT regarding IOP-lowering effect in patients with primary or secondary OAG or patients with OHT when used in laser naïve eyes. Repeat SLT had an equivalent IOP reduction efficacy compared with primary SLT though this has mostly been studied in case series with methodological limitations. No study has reported about the comparison of the efficacy of SLT versus ALT in patients who have received primary SLT. Baseline IOP as the prognostic factor for SLT or ALT success has been confirmed by a large number of studies. Nevertheless, the previous studies drew divergent conclusions of the association between some other factors and the efficacy of laser trabeculoplasty. Therefore, it is reasonable to evaluate other potentially influential factors for the treatment success in this thesis.
Chapter 3 Methods

In this chapter, five sections are included. Section 3.1 presents the basic information extracted from the protocol of the Repeat Laser Study to specify how the original data was created. Section 3.2 describes the data cleaning procedures. Methods of the primary outcome, secondary outcomes and subgroup analyses are reported in Section 3.3 along with sensitivity analyses. Section 3.4 illustrates the development and assessment of the prediction model for laser success. Section 3.5 is a summary.

3.1 Basic information of the Repeat Laser Study

Trial design
The Repeat Laser Study is a multicenter, patient-masked, randomised, parallel-group, active-controlled, equivalence trial in seven academic hospitals from seven cities of Canada: Halifax, Toronto, London, Edmonton, Calgary, Hamilton, and Montreal.

Participants
Inclusion criteria:

- Equal to or more than 18 years of age;
- Primary open-angle glaucoma (POAG), pigmentary dispersion syndrome (PDS) pseudoexfoliation syndrome (PXF), or ocular hypertension (OHT);
- Previous 360-degree SLT;
- Intraocular pressure (IOP) greater than 16 mmHg on at least two different days within one month;
- Both of the eyes had to have best-corrected visual acuity at least 20/200;
- If the patients were treated in two eyes, the first treated eye (usually the eye with higher IOP) decided by the physician will be recruited in the study;
- Willing to participate.

Exclusion criteria:

- Secondary open-angle glaucoma (other than PDG and PXF) or narrow-angle
glaucoma (defined as the anterior trabecular meshwork is not visible 360 degrees);

- Previous non-laser glaucoma surgery;
- Intraocular surgery is anticipated in the 12 months after laser treatment;
- Corneal disease which can obscure acceptable visualization of the trabecular meshwork or can create an unreliable IOP measurements;
- Topical or systematic steroids is used at present or systematic steroid is prospected to be used in the 6 months after laser treatment;
- Previous ALT treatment;
- Pregnant or breastfeeding females.

**Settings and locations**

Eligible patients were identified and recruited by glaucoma specialists in their practices, where the laser was performed.

**Randomisation and allocation**

The randomisation and allocation schedule was generated by the study coordinating centre in the Ivey Eye Institute at University of Western Ontario with the technical support from the Lawson Research Kidney Research Unit, LHSC, London Ontario. Randomisation was phone-based by the Lawson Research Kidney Research Unit. A randomised block of 4, 6, 8 at each centre was conducted. Participants were randomised with 1:1 allocation ratio to either SLT or ALT according to the allocation schedule created by the software (STATA, College Station Texas).

After the enrolment of the patients by the local ophthalmologist, the site based study coordinator accessed the randomised allocation and informed the ophthalmologist. The participants and the technicians responsible for IOP, visual acuity, and central corneal thickness (CCT) tests were masked to the type of laser treatment. Treatment allocation was not blinded for the persons who were responsible for the data analysis.

**Procedures**

Basic information of participants, including demographics, glaucoma risk factors, medical history, and concomitant medications, were recorded at the baseline visit.
Before laser treatment in the study, baseline IOP was the average of at least three IOP measurements taken on two separate days within one month. When measuring IOP, Goldmann applanation tonometer was used. The mire and dial were read by different people. IOP at each measurement was taken two times if the difference was within 2 mmHg. If the difference was $\geq 3$ mmHg, the third measurement was taken, and the median of the three measurements was used for data analysis.

Other baseline measurements included best-corrected visual acuity (BCVA) with Snellen chart, a slit-lamp assessment for the anterior segment, stereoscopic optic nerve exam, central corneal thickness (CCT) with ultrasound pachymetry, and gonioscopy with goniolens. Anterior chamber inflammation was recorded as cell scoring: $0 = 0$ cell, $+0.5 = 1$ to 5 cells (trace), $+1 = 6$ to 15 cells, $+2 = 16$ to 25 cells, $+3 = 26$ to 50 cells, $+4 \geq 50$ cells; and flare scoring: $0 =$ none, $1 =$ faint, $+2 =$ moderate, $+3 =$ marked, $+4 =$ intense. The gonioscopy grading used the Modified Shaffer grading based on the most visible angle structure: $0 =$ closed, grade 1 = Schwalbe’s line visible, grade 2 = trabecular meshwork, grade 3 = scleral spur, grade 4 = ciliary body band. The pigment of trabecular meshwork was graded as: $0 =$ none, $1 =$ light, $2 =$ medium, $3 =$ dark brown, $4 =$ almost black. Peripheral anterior synechiae were recorded as present or absent.

Consenting and baseline eye examination was preferably on the same day or at most within one week before the laser treatment. Before the laser therapy, IOP was measured. The recruited patient received either SLT or ALT treatment. Before and after the laser treatment, 0.15% brimonidine was used in the treatment eye. The inferior 180-degree of trabecular meshwork was treated. Selecta 7000 was used for SLT. The laser was standardised with 400-μm spot size and 3-ns duration, and it was centred on the trabecular meshwork with 50 non-overlapping applications. The starting energy was 0.7 mJ, and then was adjusted until the bubble formation appeared, and finally was decreased by 0.1 mJ for the rest of treatment. The laser of ALT was set with 50-μm spot size, 0.1-second duration, and a power ranging from 400 to 800 mW. The ALT was performed through an antireflective coated Goldman lens with 50 applications. The energy was set to generate blanching or occasional bubble formation in the anterior trabecular meshwork.
After the laser treatment, participants completed 6 follow-up visits at the following time points: 1 hour ± 30 min, 1 week ± 2 days, 1 month ± 7 days, 3 months ± 10 days, 6 months ± 2 weeks, and 12 months ± 3 weeks.

**Outcomes**

The primary outcome of the Repeat Laser Study was IOP change from baseline to the 12-month follow-up compared between the two lasers.

The pre-specified secondary outcomes included:

- IOP change from baseline to every post-laser visit except for the post-laser 1-hour measurement;
- Success of laser treatment. Success was defined as a IOP reduction of more than 2 mmHg from baseline;
- Snellen visual acuity, which was converted to LogMAR unit, at every post-laser visit;
- Proportion of absence of anterior chamber inflammation at every post-laser visit;
- Proportion of trabecular meshwork pigmentation graded 2 to 4 at 12-month follow-up visit;
- Number of glaucoma medications needed per patient at 12-month follow-up visit;
- Glaucoma surgery during 12-month follow-up;
- IOP spike, which was defined as an elevation of IOP > 5 mmHg at 1 hour.

**Sample size**

The sample size calculation was based on the IOP change from baseline to the 12-month follow-up. Equivalence was claimed if the 95% confidence interval of the mean difference between two treatment groups lies within -3 mmHg and +3 mmHg. The margin was pre-decided by the study group based on the clinically meaningful difference along with previous statistical outcomes and feasibility. It was not usual that the glaucoma treatment strategy will change with less than 3 mmHg difference of IOP. Also, it was recommended by the FDA that the margin should be less than the effect of active control treatment. Previous studies showed ALT reduced baseline IOP by approximately 3.2 to 9.6 mmHg at 12 months. Therefore, choosing 3 mmHg as the equivalence
margin was satisfied with the FDA guideline. Assuming a 90% chance with Type I error rate of 0.05 that a 95% confidence interval can exclude a difference of more than 3 mmHg, which was determined as the clinically meaningful difference, the trial would need to recruit 117 eyes totally. Enrolling approximately 137 eyes would allow for 10% protocol violation and loss to follow-up.

Data collection
Data were recorded on standardised paper forms by the research coordinators, and then the data was inputted to the web-based data system.

3.2 Data cleaning

Recheck data entry accuracy and correct errors
The records in the paper forms and the study website were compared for 14 (10%) of the 137 randomised participants consecutively treated in the Ivey Eye Institute, London, ON. Approximately 314 inputs for each patient, namely 4396 inputs in total, were compared.

There were 11 of 4396 (0.3%) missing values and 32 of 4396 (0.7%) errors. On average, approximately 3 missing values or errors were found per participant. The most common errors were seen in history documentation (10 missing values, 5 errors in previous IOP records, and 5 other errors) and visual acuity test (12 errors). IOP measurement values were wrong in 3 inputs. Other errors were identified in laser parameters, anterior chamber inflammation, and trabecular meshwork pigmentation data. The details of errors and missing values are shown in Appendices 1A and 1B. All those errors and missing values were corrected before the data analyses.

Problematic data in digital data sets
Detection and correction of problematic data in the digital data sets included: searching for missing data and determining if the missing can be avoided, detecting outliers, checking inclusion and exclusion criteria, checking logic and consistency of variables recorded in different tables, recording suspected data errors, consulting study coordinators or participants for problematic data if possible, and editing suspected or confirmed error data in the following ways: deletion, correction, no change, or imputation.
Among the 111 variables used for future data analyses of the 137 patients in the digital tables, 31 errors and 8 missing values were detected and modified if possible (Appendices 2A to 2D). Since the missing rate of medication treatment time was up to 38% (Appendix 3), it suggested that this kind of information was not available. Therefore, we addressed the problem with imputation. The missing start month and start year of medications were imputed with “January” and “2000” respectively. When the stop year of medication was recorded without stop month, it was imputed with “January”. In addition, after a logic and consistency check, 17 errors were corrected (Appendix 2E and Appendix 3). Also, violation of inclusion and exclusion criteria were found in some patients, and those patients were kept in the complete case analyses (Appendix 3).

3.3 Outcome analyses

Primary and secondary outcome analyses
The primary outcome was analysed for the complete cases (modified intention-to-treat), who did not have missing data in the primary and secondary outcomes or the variables used in the prediction model. To assess the equivalence between SLT and ALT in IOP change at 12 months, the mean difference between the two laser treatments and the 95% CI was derived by an independent two-sample t-test. If the 95% CI of the mean difference between the two laser groups falls within the proposed margin of equivalence (-3 mmHg to +3 mmHg), the two types of trabeculoplasty can be claimed equivalent. Before the independent two-sample t-test was conducted, normality of the samples of the two groups was determined by visualizing the histogram. Homogeneity of variance between the two treatment groups was analysed using $F$ test.

All the secondary outcomes were also analysed based on the complete cases and tested for the superiority of SLT versus ALT. An independent two-sample t-test was used for the continuous outcomes. For the binary outcomes, results were presented as risk difference (RD) and relative risk (RR) with 95% CI. A two-sided p value < 0.05 was considered significant.

Subgroup analyses
The primary outcome was analysed in the planned subgroups, which were set up after the
assessment of the baseline characteristics:

- POAG patients
- Baseline IOP < 22 mmHg vs ≥ 22 mmHg
- Patients aged < 66 years of age vs patients ≥ 66 years of age
- Females vs males
- Patients with two or less glaucoma risk factors vs more than two glaucoma risk factors;
- CCT < 556 μm vs CCT ≥ 556 μm
- With vs without glaucoma medications at baseline
- PGAs users vs non-PGAs users at baseline (PGAs users included those who used PGAs monotherapy or PGAs fixed combination)
- CAIs users vs non-CAIs users at baseline (CAIs users included those who used CAIs monotherapy or CAIs fixed combination)
- The most recent SLT treatment ≥ 3 years vs <3 years before the study

Sensitivity analyses

The primary outcome analysis was repeated for the per-protocol population. Patients who had increased the number of medication, received a glaucoma surgery, or received another glaucoma laser treatment during the 12-month follow-up were considered protocol violation. A sensitivity test for the primary endpoint was also conducted with extreme case analysis (the best & worst case assessment), in which the missing IOP at 12 months were imputed with the minimum IOP among all the participants in the SLT group and the maximum IOP among those in the ALT group, and reverse.

3.4 Creating a regression model to explore the predictors for laser treatment success

Source of data

The data from the complete cases were used in the prediction model development.

Outcome
The outcome in the prediction model was laser treatment success, which was defined as IOP change > 2 mmHg from baseline to 12-month follow-up. The detail of IOP test is described in Section 3.1.

**Candidate predictors**
Candidate predictors were selected based on previous studies, which have found a significant association between the predictors and efficacy of laser trabeculoplasty (Section 2.3 in Chapter 2).

Candidate predictors included age (years), baseline IOP (mmHg), CCT (μm), grade of trabecular meshwork pigmentation (0-4), number of concurrent glaucoma medication (0-3), prostaglandin analogues (PGAs) users, and carbonic anhydrase inhibitors (CAIs) users. All the variables were measured and recorded before the laser treatment. The measurements were blinded, while the analyses were not blinded for the treatment allocation. In addition, all the variables were coded as quantitative variables in the regression model.

No missing values were left in the candidate predictors. Regarding the imputation for the time of medication treatment, details are provided in Section 3.2.

**Model development**
After the univariate analyses to evaluate the correlation of each candidate predictor with the outcome, a logistic regression model was created to explore the association of the potential predictors with the success of laser treatment. Predictors were selected automatically using backward stepwise method with a p value greater than 0.15 for removal. Interaction terms were not examined in such a relatively small sample size.\(^{166}\)

**Model performance**
Model performance was analysed with discrimination and calibration. Discrimination ability of the model was assessed by Receiver Operating Characteristic (ROC) curve.\(^{167}\) Hosmer-Lemeshow (H-L) goodness-of-fit test was used to test the calibration property.\(^{168}\) A significant result of H-L test suggests a poor prediction model. A calibration graph was developed to visually evaluate the agreement between predictive and observed outcomes.
Internal validation

Bootstrapping was used to assess internal validation and to correct overly optimistic measures of model fit.\textsuperscript{169} The procedure repeated 1000 times to create an estimation of the population parameter.

3.5 Summary

The data used in this thesis was obtained from a multicenter, patient-masked, randomised, parallel-group, active-controlled, equivalence trial comparing ALT and SLT in lowering IOP effect. The primary outcome was IOP change from baseline to 12-month visit. The errors or missing values of the primary or secondary outcomes were sparse in the data sets. The independent two-sample t-tests were performed to evaluate the equivalence of the primary outcome and the superiority of the secondary continuous outcomes between the two laser treatment groups. For the binary outcomes, both RD and RR were analysed. To explore the predictors for treatment success, both univariate analysis and Logistic regression analysis were conducted. Backward stepwise selection of independent variables was applied. Model performance was evaluated with ROC curve, Hosmer-Lemeshow (H-L) goodness-of-fit test, and calibration graph. Bootstrap resampling method was also used to assess the internal validity of the final model.
Chapter 4 Results

There are three sections in this chapter. Section 4.1 includes the study flow chart and describes baseline characteristics of study participants. Analyses evaluating the equivalence of treatment groups for the primary and secondary study outcomes are then summarised in Section 4.2 along with subgroup analyses and sensitivity analyses of the primary outcomes. Finally, results from a 12-month predictive model of successful IOP reduction are presented in Section 4.3.

4.1 Descriptive statistics

Data collection procedures
The first patient was recruited and received laser treatment in the study on February 14, 2013. The last patient was recruited and received laser treatment on October 24, 2016. The duration of recruitment was around 3 years and 8 months.

Of the 167 patients who had approached to participate in the study, 28 were ineligible for several reasons. Randomisation was performed for 139 patients with 69 assigned to the selective laser trabeculoplasty (SLT) group and 70 to the argon laser trabeculoplasty (ALT) group. Before receiving the allocation intervention, one patient in each group was identified not eligible (Figure 2). The baseline characteristics of these two patients were not recorded in the study database.

By June 20, 2017, when data analysis began, 128 patients had completed the 12 months after their laser treatment date. Among the 128 patients, 7 patients were withdrawn from the study for reasons, 1 patient missed one of the follow-up visits, and 5 patients had one missing value for data analysis. Therefore, 115 patients were available for the complete case analyses (Figure 2).

Baseline characteristics of participants
Among the 115 patients, over 80% were Caucasian in both groups. Around 70% were diagnosed as primary open-angle glaucoma (POAG) in both groups. The mean baseline
intraocular pressure (IOP) was comparable between the two laser groups with 21.67 mmHg in the SLT group and 21.77 mmHg in the ALT group. Best-corrected visual acuity (BCVA), modified Schaffer grade, trabecular meshwork pigmentation, peripheral anterior synechiae, cup to disc ratio, and the number of medication used at baseline were also well balanced between the two groups. Details of the baseline characteristics are shown in Table 1A and Table 1B.
Figure 2: Flow chart of the Repeat Laser Study

Table 1A: Baseline characteristics of patients in complete case analyses

<table>
<thead>
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<th></th>
<th>SLT (n = 57)</th>
<th>ALT (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centre</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western University</td>
<td>15 (26%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>University of Toronto</td>
<td>9 (16%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>University of Calgary</td>
<td>15 (26%)</td>
<td>12 (21%)</td>
</tr>
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<td>University of Alberta</td>
<td>2 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Dalhousie University</td>
<td>13 (23%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>McMaster University</td>
<td>3 (5%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td><strong>Study eye was right eye</strong></td>
<td>23 (40%)</td>
<td>37 (64%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>29 (51%)</td>
<td>34 (59%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>64.71 ± 10.85</td>
<td>66.50 ± 9.56</td>
</tr>
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<td>Range</td>
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<td>Caucasian</td>
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</tr>
<tr>
<td>African</td>
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<td>3 (5%)</td>
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<tr>
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<td>7 (12%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td><strong>BCVA (LogMAR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.10 ± 0.12</td>
<td>0.13 ± 0.23</td>
</tr>
<tr>
<td>range</td>
<td>-0.12 to 0.48</td>
<td>-0.10 to 1.00</td>
</tr>
<tr>
<td><strong>IOP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.67 ± 3.15</td>
<td>21.77 ± 3.35</td>
</tr>
<tr>
<td>range</td>
<td>16.50 to 29.50</td>
<td>15.50 to 32.50</td>
</tr>
<tr>
<td><strong>CCT (μm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>552.14 ± 37.44</td>
<td>562.59 ± 37.83</td>
</tr>
<tr>
<td>range</td>
<td>452.00 to 618.00</td>
<td>484.00 to 682.00</td>
</tr>
<tr>
<td><strong>Modified Schaffer (0-4)</strong></td>
<td>2 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30 (53%)</td>
<td>31 (53%)</td>
</tr>
<tr>
<td>4</td>
<td>25 (44%)</td>
<td>25 (43%)</td>
</tr>
<tr>
<td><strong>TMP (0-4)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (9%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>1</td>
<td>27 (47%)</td>
<td>30 (52%)</td>
</tr>
<tr>
<td>2</td>
<td>19 (33%)</td>
<td>19 (33%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (9%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>4</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>SLT (n= 57)</td>
<td>ALT (n= 58)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>PAS (Present)</strong></td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Cup to disc ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.64 ± 0.19</td>
<td>0.66 ± 0.17</td>
</tr>
<tr>
<td>Range</td>
<td>0.20 to 0.90</td>
<td>0.20 to 0.90</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History of POAG</td>
<td>21 (37%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Age (above 60)</td>
<td>41 (72%)</td>
<td>48 (83%)</td>
</tr>
<tr>
<td>Myopia</td>
<td>13 (23%)</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>Elevated IOP (above 21 mmHg)</td>
<td>38 (67%)</td>
<td>41 (71%)</td>
</tr>
<tr>
<td>Ethnic Background (labeled as “yes” if not Caucasian)</td>
<td>9 (16%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Concomitant medical conditions (hypertension, diabetes, hypothyroidism)</td>
<td>15 (26%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Number of glaucoma medication used at baseline**

<table>
<thead>
<tr>
<th>Number of glaucoma medication used at baseline</th>
<th>SLT (n= 57)</th>
<th>ALT (n= 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26 (46%)</td>
<td>28 (48%)</td>
</tr>
<tr>
<td>1</td>
<td>16 (28%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>2</td>
<td>13 (23%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (4%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

**Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SLT (n= 57)</th>
<th>ALT (n= 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POAG</td>
<td>41 (72%)</td>
<td>40 (69%)</td>
</tr>
<tr>
<td>PDS</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>PXF</td>
<td>7 (12%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>OHT</td>
<td>5 (9%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>PXF &amp; OHT</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; ACI: anterior chamber inflammation; BCVA: best-corrected visual acuity; CCT: central corneal thickness; IOP: intraocular pressure; OD: oculus dexter (right eye); OHT (OHT was defined as IOP > 21 mmHg, open drainage angles observed on gonioscopy without glaucomatous optic disc damage, detectable nerve fibre layer defect, or visual field loss.): ocular hypertension; OS: oculus sinister (left eye); PAS: peripheral anterior synechiae; PDS: pigmentary dispersion syndrome; POAG: primary open-angle glaucoma; PXF: pseudoexfoliation syndrome; SD: standard deviation; SLT: selective laser trabeculoplasty; TMP: trabecular meshwork pigmentation.
The mean ± SD actual spot size was 403.51±18.56 \( \mu m \) (range: 400 to 500 \( \mu m \)) for SLT and 52.17±4.36 \( \mu m \) (range: 50 to 66 \( \mu m \)) for ALT. The mean duration was 3 ns for SLT and 0.1 seconds for ALT as planned. The actual mean ± SD number of laser application was 50.33±1.53 (range: 46 to 58) in the SLT group and 51.60±3.41 (range: 50 to 70) in the ALT group. The mean ± SD total energy was 46.82±9.64 mJ (range: 25 to 70 mJ) for SLT treatment and 3286.77±513.54 mW (range: 2000 to 4000 mW) for ALT treatment. It should be noted that because the lasers are fundamentally different, we would not expect the laser parameters to be the same in each group.

The actual timing of observations after the laser treatment had a larger deviation in the ALT group than the SLT group at post-laser 1 hour, 1 week, 6 months, and 12 months (Table 2. and Figure 3).
Table 2: Follow-up schedule and actual follow-up time

<table>
<thead>
<tr>
<th>Schedule</th>
<th>1 hour±30 minutes</th>
<th>1 week±2 days</th>
<th>1 month±7 days</th>
<th>3 months±10 days</th>
<th>6 months±2 weeks</th>
<th>12 months ±3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLT</strong></td>
<td>1 hour±13 minutes</td>
<td>1 week±1 day</td>
<td>1 month±5 days</td>
<td>3 months±9 days</td>
<td>6 months±2 weeks</td>
<td>12 months±2 weeks</td>
</tr>
<tr>
<td></td>
<td>(30 to 104 minutes)</td>
<td>(5 to 12 days)</td>
<td>(2 to 7 weeks)</td>
<td>(9 to 17 weeks)</td>
<td>(5 to 9 months)</td>
<td>(11 to 14 months)</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>1 hour±32 minutes</td>
<td>1 week±4 days</td>
<td>1 month±5 days</td>
<td>3 months±9 days</td>
<td>6 months±3 weeks</td>
<td>12 months±3 weeks</td>
</tr>
<tr>
<td></td>
<td>(30 to 265 minutes)</td>
<td>(4 to 38 days)</td>
<td>(3 to 6 weeks)</td>
<td>(10 to 17 weeks)</td>
<td>(3 to 9 months)</td>
<td>(11 to 16 months)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; SLT: selective laser trabeculoplasty. Note: data are presented as mean±standard deviation (range).
Figure 3: Timing of observations in the Repeat Laser Study

Note: Each row represents a randomised patient in the study; the dots correspond to the actual date of the follow-up visits after the laser treatment.

4.2 Analyses of the outcomes

Primary outcome (IOP change from baseline to the 12-month follow-up)
Among the 115 patients with complete data, the mean change of IOP from baseline to 12 months was 3.35 mmHg (95% CI, 2.03 to 4.66 mmHg) in the SLT group and 3.35 mmHg (95% CI, 2.03 to 4.69 mmHg) in the ALT group, with a difference of -0.01 mmHg (95% CI, -1.86 to 1.84 mmHg). The 95% CI of the difference of IOP change was within the equivalence range of the -3 to +3 mmHg boundary. (Table 3 and Figure 4)
Table 3: IOP change (mmHg) from baseline to the 12-month visit

<table>
<thead>
<tr>
<th></th>
<th>SLT N, mean(SD)</th>
<th>ALT N, mean(SD)</th>
<th>Difference of the IOP change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete case analysis</td>
<td>57, 3.35 (4.96)</td>
<td>58, 3.36 (5.06)</td>
<td>-0.01 (-1.86 to 1.84)</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td>46, 3.43 (3.87)</td>
<td>38, 2.87 (3.15)</td>
<td>0.56 (-0.99 to 2.12)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CI: confidence interval; IOP: intraocular pressure; SD: standard deviation; SLT: selective laser trabeculoplasty.

Figure 4: Difference of mean IOP change (mmHg) from baseline to the 12-month visit between the ALT and SLT group

ALT: argon laser trabeculoplasty; CI: confidence interval; IOP: intraocular pressure; SLT: selective laser trabeculoplasty. Two dash lines represent the clinical equivalence range.

Secondary outcomes

IOP change from baseline to different post-laser visits

The IOP reductions at one week and one month after the laser treatment were greater in the SLT group compared to the ALT group. The 95% CIs of the IOP change difference between the two treatment groups at post-laser treatment 3 months and 6 months were within the equivalent boundary (Table 4, Figure 5).
Table 4: IOP change (mmHg) from baseline to different time points

<table>
<thead>
<tr>
<th></th>
<th>SLT (n = 57) mean (SD)</th>
<th>ALT (n= 58) mean (SD)</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>3.23 (4.53)</td>
<td>1.42 (3.56)</td>
<td>1.82 (0.31 to 3.32)</td>
<td>0.02*</td>
</tr>
<tr>
<td>1 month</td>
<td>4.69 (3.84)</td>
<td>2.81 (3.66)</td>
<td>1.88 (0.50 to 3.27)</td>
<td>0.01*</td>
</tr>
<tr>
<td>3 months</td>
<td>4.34 (2.97)</td>
<td>3.43 (4.81)</td>
<td>0.91 (-0.57 to 2.40)</td>
<td>0.22</td>
</tr>
<tr>
<td>6 months</td>
<td>3.28 (3.73)</td>
<td>3.50 (4.08)</td>
<td>-0.22 (-1.66 to 1.22)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; BCVA: best corrective visual acuity; CI: confidence interval; IOP: intraocular pressure; SD: standard deviation; SLT: selective laser trabeculoplasty. * indicates a p value < 0.05. Data were analysed based on complete cases.

Figure 5: IOP at different time points

ALT: argon laser trabeculoplasty (n= 58); CI: confidence interval.; IOP: intraocular pressure; SLT: selective laser trabeculoplasty (n = 57). Data were analysed based on complete cases.

Laser success rate at different post-laser visits

The success of laser treatment was defined as IOP reduction greater than 2 mmHg from baseline. The success rate was between 61% to 81% in the SLT group and 43% to 64% in the ALT group during the 12-month follow-up. At the 1-week, 1-month, and 3-month
post-laser visit, the success rate was significantly greater in the SLT group than the ALT group (Table 5).

**Table 5: Number of patients with treatment success (an IOP reduction more than 2 mmHg from baseline) at different time points**

<table>
<thead>
<tr>
<th></th>
<th>SLT (n=57)</th>
<th>ALT (n=58)</th>
<th>RD (95% CI, p)</th>
<th>RR (95% CI, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>37 (65%)</td>
<td>25 (43%)</td>
<td>0.22 (0.04 to 0.40, 0.02)*</td>
<td>1.51 (1.06 to 2.14, 0.02)*</td>
</tr>
<tr>
<td>1 month</td>
<td>44 (77%)</td>
<td>34 (59%)</td>
<td>0.19 (0.02 to 0.35, 0.03)*</td>
<td>1.32 (1.02 to 1.71, 0.04)*</td>
</tr>
<tr>
<td>3 months</td>
<td>46 (81%)</td>
<td>36 (62%)</td>
<td>0.19 (0.02 to 0.35, 0.03)*</td>
<td>1.30 (1.02 to 1.65, 0.03)*</td>
</tr>
<tr>
<td>6 months</td>
<td>35 (61%)</td>
<td>37 (64%)</td>
<td>-0.02 (-0.20 to 0.15, 0.79)</td>
<td>0.96 (0.72 to 1.28, 0.79)</td>
</tr>
<tr>
<td>12 months</td>
<td>37 (65%)</td>
<td>36 (62%)</td>
<td>0.03 (-0.15 to 0.20, 0.75)</td>
<td>1.05 (0.79 to 1.38, 0.75)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CI: confidence interval; IOP: intraocular pressure; RD: risk difference; RR: relative risk; SLT: selective laser trabeculoplasty. * indicates a p value < 0.05.

Data were analysed based on complete cases.

**Best-corrected visual acuity (BCVA) at each visit**

The mean BCVA was comparable between the two laser treatment groups at all the follow-up visits (Table 6).
### Table 6: BCVA (LogMAR) at different time points

<table>
<thead>
<tr>
<th></th>
<th>SLT (n=57)</th>
<th>ALT (n=58)</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.10 (0.12)</td>
<td>0.13 (0.23)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1 hour</td>
<td>0.13 (0.14)</td>
<td>0.15 (0.26)</td>
<td>-0.02 (-0.10 to 0.05)</td>
<td>0.57</td>
</tr>
<tr>
<td>1 week</td>
<td>0.09 (0.12)</td>
<td>0.11 (0.22)</td>
<td>-0.03 (-0.09 to 0.04)</td>
<td>0.46</td>
</tr>
<tr>
<td>1 month</td>
<td>0.09 (0.12)</td>
<td>0.13 (0.22)</td>
<td>-0.04 (-0.11 to 0.02)</td>
<td>0.20</td>
</tr>
<tr>
<td>3 months</td>
<td>0.09 (0.16)</td>
<td>0.11 (0.22)</td>
<td>-0.02 (-0.09 to 0.05)</td>
<td>0.55</td>
</tr>
<tr>
<td>6 months</td>
<td>0.09 (0.14)</td>
<td>0.13 (0.24)</td>
<td>-0.03 (-0.11 to 0.04)</td>
<td>0.39</td>
</tr>
<tr>
<td>12 months</td>
<td>0.07 (0.13)</td>
<td>0.13 (0.25)</td>
<td>-0.06 (-0.14 to 0.01)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; BCVA: best-corrected visual acuity; CI: confidence interval; SD: standard deviation; SLT: selective laser trabeculoplasty. Data were analysed based on complete cases.

**Anterior chamber inflammation at each visit**

Eleven (19%) patients in the SLT group and 12 (21%) patients in the ALT group used the topical steroid to control post-laser anterior chamber inflammation. About 70% patients had anterior chamber inflammation at 1 hour after the laser treatments. The mean ± SD anterior chamber cells grade at post-laser one hour was 0.51 ± 0.48 (range 0 to 2) in the SLT group and 0.32 ± 0.28 (range 0 to 1) in the ALT group. The difference was significant with p = 0.01 (mean difference, 0.19; 95% CI, 0.05 to 0.33). The percentage of patients with cleared ocular inflammation (cell grade 0 and flare grade 0) was significantly lower in the SLT group than the ALT group at post-laser 1 week. The proportion was comparable between the two groups at the rest of the visit time points (Table 7).
Table 7: Number of patients without anterior chamber inflammation at different time points

<table>
<thead>
<tr>
<th></th>
<th>SLT (n=57)</th>
<th>ALT (n=58)</th>
<th>RD (95% CI, p)</th>
<th>RR (95% CI, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>56 (98%)</td>
<td>58 (100%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1 hour</td>
<td>15 (26%)</td>
<td>21 (36%)</td>
<td>-0.10 (-0.27 to 0.07, 0.25)</td>
<td>0.73 (0.42 to 1.27, 0.26)</td>
</tr>
<tr>
<td>1 week</td>
<td>43 (75%)</td>
<td>54 (93%)</td>
<td>-0.18 (-0.31 to -0.05, 0.01)*</td>
<td>0.81 (0.69 to 0.96, 0.01)*</td>
</tr>
<tr>
<td>1 month</td>
<td>53 (93%)</td>
<td>56 (97%)</td>
<td>-0.04 (-0.12 to 0.05, 0.39)</td>
<td>0.96 (0.88 to 1.05, 0.39)</td>
</tr>
<tr>
<td>3 months</td>
<td>55 (96%)</td>
<td>58 (100%)</td>
<td>-0.04 (-0.08 to 0.01, 0.15)</td>
<td>0.96 (0.92 to 1.01, 0.16)</td>
</tr>
<tr>
<td>6 months</td>
<td>57 (100%)</td>
<td>57 (98%)</td>
<td>0.02 (-0.02 to 0.05, 0.32)</td>
<td>1.02 (0.98 to 1.05, 0.32)</td>
</tr>
<tr>
<td>12 months</td>
<td>55 (96%)</td>
<td>57 (98%)</td>
<td>-0.02 (-0.08 to 0.04, 0.55)</td>
<td>0.98 (0.92 to 1.04, 0.55)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CI: confidence interval; RD: risk difference; RR: relative risk; SLT: selective laser trabeculoplasty. * indicates a p value < 0.05. Data were analysed based on complete cases.

Trabecular meshwork pigmentation at the 12-month follow-up visit

The proportion of trabecular meshwork pigmentation greater than Grade 1 was 40% versus 38% at the 12-month follow-up in the SLT group versus the ALT group. The risk difference (RD) and relative risk (RR) were not significant between the two laser treatment groups at the 12-month visit (Table 8).

Table 8: Number of trabecular meshwork pigmentation greater than Grade 1 at baseline and at 12 months

<table>
<thead>
<tr>
<th></th>
<th>SLT (n=57)</th>
<th>ALT (n=58)</th>
<th>RD (95% CI, p)</th>
<th>RR (95% CI, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25 (44%)</td>
<td>22 (38%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>12 months</td>
<td>23 (40%)</td>
<td>22 (38%)</td>
<td>0.02 (-0.15 to 0.20, 0.79)</td>
<td>1.06 (0.67 to 1.68, 0.79)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CI: confidence interval; RD: risk difference; RR: relative risk; SLT: selective laser trabeculoplasty. Data were analysed based on complete cases.
Number of glaucoma medications needed per patient at 12-month follow-up visit

The number of glaucoma medications used at 12 months was comparable between the two laser treatment groups (Table 9).

**Table 9: Number of medication used per person at baseline and at 12 months**

<table>
<thead>
<tr>
<th></th>
<th>SLT (n = 57) mean(SD)</th>
<th>ALT (n= 58) mean(SD)</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.84 (0.90)</td>
<td>0.93 (1.04)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>12 months</td>
<td>1.07 (0.96)</td>
<td>1.24 (1.06)</td>
<td>-0.17 (-0.55 to 0.20)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CI: confidence interval; SLT: selective laser trabeculoplasty.

Data were analysed based on complete cases.

**Glaucoma surgery during 12-month follow-up**

One patient (2%) in the SLT group and 4 (7%) in the ALT group progressed to surgery (laser trabeculoplasty, iStent, trabeculectomy, or more than one of those kinds of surgery) during the 12-month follow-up. The RD was -0.05 (95% CI -0.13 to 0.02; p = 0.18), and RR was 0.25 (95% CI, 0.03 to 2.23; p = 0.22) between the SLT and ALT group.

**IOP spike**

IOP spike, which was defined as an elevation of IOP > 5 mmHg from baseline, was found in 0/57 (0%) and 0/58 (0%) patient in the SLT and ALT groups respectively at the post-laser 1-hour test.

**Subgroup analyses**

The subgroup analyses based on diagnosis of POAG, baseline IOP, age, gender, glaucoma risk factors, central corneal thickness (CCT), number of glaucoma medicine used at baseline, prostaglandins analogues (PGAs) users, carbonic anhydrase inhibitors (CAIs) users, and time of previous SLT showed an equivalent IOP reduction effect or a non-significant IOP change difference at 12 months between the SLT and ALT group (Table 10 Figure 6).
Table 10: IOP change (mmHg) from baseline to the 12-month visit in subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>SLT N, mean(SD)</th>
<th>ALT N, mean(SD)</th>
<th>Mean Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POAG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline IOP &lt; 22 mmHg</td>
<td>33, 2.67 (2.88)</td>
<td>32, 2.05 (3.72)</td>
<td>0.61 (-1.03 to 2.26)</td>
</tr>
<tr>
<td>Baseline IOP ≥ 22 mmHg</td>
<td>24, 4.28 (6.84)</td>
<td>26, 4.96 (6.02)</td>
<td>-0.68 (-4.34 to 2.98)</td>
</tr>
<tr>
<td><strong>Age &lt; 66 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 66 years</td>
<td>30, 3.28 (3.25)</td>
<td>27, 2.25 (4.61)</td>
<td>1.02 (-1.08 to 3.13)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29, 3.97 (4.04)</td>
<td>34, 3.76 (5.34)</td>
<td>0.20 (-2.22 to 2.62)</td>
</tr>
<tr>
<td><strong>Glaucoma risk factors ≤ 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma risk factors &gt; 2</td>
<td>25, 4.06 (5.78)</td>
<td>33, 2.82 (4.45)</td>
<td>-0.21 (-2.50 to 2.07)</td>
</tr>
<tr>
<td><strong>CCT &lt; 556 μm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCT ≥ 556 μm</td>
<td>30, 4.05 (4.67)</td>
<td>27, 3.64 (5.74)</td>
<td>0.41 (-2.35 to 3.18)</td>
</tr>
<tr>
<td><strong>No glaucoma medicine used at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one glaucoma medicine used at baseline</td>
<td>31, 3.62 (4.69)</td>
<td>30, 2.41 (6.37)</td>
<td>1.21 (-1.65 to 4.07)</td>
</tr>
<tr>
<td><strong>Using PGAs at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not using PGAs at baseline</td>
<td>31, 3.98 (5.87)</td>
<td>33, 3.91 (3.19)</td>
<td>0.07 (-2.27 to 2.42)</td>
</tr>
<tr>
<td><strong>Using CAIs at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not using CAIs at baseline</td>
<td>43, 3.93 (5.24)</td>
<td>39, 3.46 (3.19)</td>
<td>0.47 (-1.46 to 2.40)</td>
</tr>
<tr>
<td><strong>Previous SLT &lt; 3 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous SLT ≥ 3 years</td>
<td>26, 3.25 (4.66)</td>
<td>30, 2.50 (5.79)</td>
<td>0.76 (-2.09 to 3.60)</td>
</tr>
</tbody>
</table>

ALT: argon laser trabeculoplasty; CAIs: Carbonic anhydrase inhibitors; CCT: central corneal thickness; CI: confidence interval; IOP: intraocular pressure; PGAs: prostaglandin analogues; POAG: primary open-angle glaucoma; SLT: selective laser trabeculoplasty. Data were analysed based on complete cases.
Figure 6: Difference of mean IOP change from baseline to the 12-month visit between SLT and ALT in subgroups

ALT: argon laser trabeculoplasty; CAIs: Carbonic anhydrase inhibitors; CCT: central corneal thickness; CI: confidence interval; IOP: intraocular pressure; PGAs: prostaglandin analogues; POAG: primary open-angle glaucoma; SLT: selective laser trabeculoplasty. Data were analysed based on complete cases. Two dash lines represent the clinical equivalence range.
Sensitivity analyses for the primary outcome

- Per-protocol analysis

Among the 115 patients with complete data, 31 patients were considered protocol deviations (4 underwent surgery or laser trabeculoplasty during the 12-month follow-up; 26 added at least one additional glaucoma medication during 12-month follow-up; 1 had both of the above reasons). Therefore, 84 patients remained in the per-protocol analysis.

Among the 84 protocol-adhering patients, the mean IOP reduction was greater in the SLT group with a difference of 0.56 mmHg (95% CI, -0.99 to 2.12 mmHg; p = 0.47) compared with the ALT group. The 95% CI of the difference of IOP change was within the equivalence range of the -3 to +3 mmHg boundary (Table 3, Figure 4).

- Extreme case analyses

For the 128 patients, who were at the date more than 12 months after the laser treatment by June 2017, two extreme case analyses were conducted. Among those patients, 121 patients had the 12-month visit, and the 12-month IOP ranged between 8.5 to 38 mmHg. In the rest of 7 patients who did not have the 12-month visit, 4 were in the SLT group, and 3 were in the ALT group. If the IOP were imputed with 8.5 mmHg for the 4 patients in the SLT group and with 38 mmHg for the 3 patients in the ALT group, the difference of mean IOP change between the two groups was -1.34 mmHg (95% CI, -3.5 to 0.82; p = 0.22). In reverse, when the IOP was imputed with 38 mmHg for the SLT patients and 8.5 mmHg for the ALT patients, the difference was 1.89 mmHg (95% CI -0.23 to 4.02; p = 0.08). Both the extreme case analyses did not show a significant difference of IOP change between the two treatment groups.

Diagnostic test for the primary outcome before the independent two-sample t-test for the complete case analysis

The histograms of the IOP change from baseline to 12 months for the two treatment groups are shown in Figure 7, which suggests a proximally normal distribution of the two samples. The test for homogeneity of the standard deviation of the IOP change between the two groups was not significant with p=0.88.
Figure 7: Histograms of IOP change from baseline to the 12-month visit in the ALT and SLT group based on complete cases

4.3 Prediction model

Model development

In the 115 patients included in complete case analyses, 73 (63%) had a successful IOP reduction outcome at the 12-month follow-up (Table 11). The baseline characteristics are presented in Table 1A, 1B, and Table 11.

In the model development process, 7 potential variables were evaluated. No missing data in the predictors and the outcome was encountered. The unadjusted analyses showed the IOP at baseline had a significant positive association with treatment success at 12 months (odds ratio 1.17; 95% CI, 1.02 to 1.34; p = 0.02). Using the p = 0.15 as the cut-off point in the backward variable selection, baseline IOP and number of glaucoma medications used at baseline were kept in the final model. The odds ratio (OR) in the final model and the model optimized after bootstrap method are shown in Table 11.
The optimized final model was expressed as

$$\log \left( \frac{P_{\text{success}}}{1-P_{\text{success}}} \right) = -2.74 + 0.17 \text{ baseline IOP} - 0.46 \text{ number of glaucoma medications}$$

where $P_{\text{success}}$ represented the probability of treatment success at 12 months. Note also that baseline IOP (mmHg) and number of glaucoma medications were modeled as quantitative predictors.
### Table 11: Unadjusted and adjusted association between each potential baseline predictor and outcome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Success (n = 73)</th>
<th>No success (n = 42)</th>
<th>Univariate OR (95% CI, p)</th>
<th>Multivariable OR after backward selection (95% CI, p)</th>
<th>Multivariable OR after bootstrap (95% CI, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>66.10 (10.18)</td>
<td>64.78 (10.33)</td>
<td>1.01 (0.98 to 1.05, 0.50)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IOP, mmHg</td>
<td>22.25 (3.35)</td>
<td>20.79 (2.83)</td>
<td>1.17 (1.02 to 1.34, 0.02)</td>
<td>1.19 (1.04 to 1.36, 0.01)</td>
<td>1.19 (1.03 to 1.38, 0.02)</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>558.45 (32.49)</td>
<td>555.60 (46.06)</td>
<td>1.00 (0.99 to 1.01, 0.70)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>TMP, 0 to 4</td>
<td>1.44 (0.82)</td>
<td>1.36 (0.82)</td>
<td>1.13 (0.71 to 1.82, 0.61)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Glaucoma medication, n</td>
<td>0.75 (0.91)</td>
<td>1.12 (1.04)</td>
<td>0.68 (0.46 to 1.01, 0.05)</td>
<td>0.63 (0.41 to 0.96, 0.03)</td>
<td>0.63 (0.40 to 1.00, 0.05)</td>
</tr>
<tr>
<td>PGAs users, n</td>
<td>28 (38%)</td>
<td>23 (55%)</td>
<td>0.51 (0.24 to 1.11, 0.09)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CAIs users, n</td>
<td>17 (23%)</td>
<td>16 (38%)</td>
<td>0.49 (0.22 to 1.13, 0.09)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

CAIs: Carbonic anhydrate inhibitors; CCT: central corneal thickness; CI: confidence interval; IOP: intraocular pressure; OR: Odds ratio; PGAs: prostaglandin analogues; TMP: trabecular meshwork pigmentation. Data are presented as mean (standard deviation) or number (%) in the first two columns. Data were analysed based on complete cases.
Model performance
The final model produced an AUC of 0.68 in the ROC curve (Figure 8). The Hosmer-Lemeshow goodness of fit test for calibration showed a non-significant discrepancy between the number of expected outcomes and the number of observed outcomes with $p = 0.21$ (Table 12). Also, the calibration plot showed a satisfied prediction (Figure 9).

Figure 8: Receiver-operating characteristic (ROC) curve for prediction of success at 12 months after the laser treatment
Table 12: Hosmer-Lemeshow test for calibration of the prediction model for treatment success

<table>
<thead>
<tr>
<th>Group</th>
<th>Range of probability (%)</th>
<th>N</th>
<th>Observed success, n (%)</th>
<th>Predicted success, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.0 - 40.6</td>
<td>12</td>
<td>6 (50.0)</td>
<td>4.3 (35.7)</td>
</tr>
<tr>
<td>2</td>
<td>41.4 - 49.9</td>
<td>11</td>
<td>4 (36.4)</td>
<td>5.0 (45.8)</td>
</tr>
<tr>
<td>3</td>
<td>52.1 - 57.2</td>
<td>12</td>
<td>4 (33.3)</td>
<td>6.6 (55.0)</td>
</tr>
<tr>
<td>4</td>
<td>58.5 - 62.6</td>
<td>11</td>
<td>9 (81.8)</td>
<td>6.6 (59.8)</td>
</tr>
<tr>
<td>5</td>
<td>63.4 - 66.6</td>
<td>14</td>
<td>7 (50.0)</td>
<td>9.0 (64.5)</td>
</tr>
<tr>
<td>6</td>
<td>67.1 - 69.1</td>
<td>15</td>
<td>10 (66.7)</td>
<td>10.2 (68.3)</td>
</tr>
<tr>
<td>7</td>
<td>70.3 - 71.0</td>
<td>6</td>
<td>5 (83.3)</td>
<td>4.3 (70.9)</td>
</tr>
<tr>
<td>8</td>
<td>71.4 - 76.0</td>
<td>12</td>
<td>11 (91.7)</td>
<td>8.9 (74.4)</td>
</tr>
<tr>
<td>9</td>
<td>77.5 - 80.4</td>
<td>12</td>
<td>8 (66.7)</td>
<td>9.5 (78.9)</td>
</tr>
<tr>
<td>10</td>
<td>81.6 - 91.4</td>
<td>10</td>
<td>9 (90.0)</td>
<td>8.6 (85.8)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 10.82, \text{ df} = 8, p = 0.21 \]
Figure 9: Predicted probabilities based on the prediction model and observed proportions of individuals with treatment success (intraocular pressure change more than 2 mmHg from baseline to the 12-month visit)
Chapter 5 Discussion

In this chapter, the findings in this thesis and the comparisons of our outcomes with previous studies are described in Section 5.1. In Section 5.2 and 5.3, the strengths and limitations are presented and justified. Conclusions and clinical implications are summarised in Section 5.4. Finally, Section 5.5 provides some ideas for future studies.

5.1 Findings

The main purpose of this thesis was to evaluate the equivalence of IOP reduction effect between SLT and ALT for those patients who had previous 360-degree SLT treatment while naïve to ALT or glaucoma surgery. Data were extracted from a multicentre randomised controlled trial (RCT) registered as “A randomized clinical trial of selective laser trabeculoplasty (SLT) in open-angle glaucoma who had been previously treated with complete SLT” with an acronym of Repeat Laser Study. The patients were recruited from seven hospitals in different cities across Canada.

By June 2017, when the data was collected for thesis analyses, 115 patients had finished the 12-month follow-up visit without missing data in all the primary and secondary outcomes. Over 80% were Caucasian, and the mean age was approximately 65 years with a mean baseline IOP of approximately 22 mmHg. The demographic characteristics and ophthalmic examinations at baseline were well balanced between the SLT and ALT treatment arms as shown in Table 1A and 1B in Chapter 4.

Efficacy

The IOP reduction from baseline to 12-month visit was equivalent between the SLT and ALT treatment based on either complete case analysis or per-protocol analysis. The mean change was 3.35 mmHg (SD 4.96) in the SLT group and 3.36 mmHg (SD 5.06) in the ALT group in the 115 complete case cohort (Table 3 in Chapter 4).

The IOP-lowering outcomes are less than the results presented by Damji et al., who reported a mean (SD) IOP decrease of 5.7 (5.63) and 6.0 (4.51) mmHg in the SLT group...
and the ALT group respectively. The study of Damji et al. and the Repeat Laser Study both applied laser on 180-degree trabecular meshwork and had comparable baseline characteristics of participants. The IOP change in the Repeat Laser Study is also less than the meta-analysis outcome reported by Wang et al., whose study summarised the outcomes from two randomised clinical trials (RCTs) with meta-analysis. The synthesized mean IOP reduction at post-laser 12 months was 4.65 mmHg after SLT and 4.31 mmHg after ALT. Both the results of Damji et al. and Wang et al. were obtained from laser naïve patients, which may explain some of the discrepancies. In addition, it suggests that repeated SLT or ALT based on previous 360-degree SLT is about 50% to 70% as efficacious as the primary laser treatment at 12-month follow-up.

The outcomes of the Repeat Laser Study also demonstrate some difference with other studies regarding the efficacy of repeat SLT. In this study, the first SLT was performed on 360-degree trabecular meshwork with approximately 100 shots on average while the second SLT was applied on 180-degree trabecular meshwork with approximately 50 shots on average. In two previous studies, the primary and secondary SLT were both applied on 360-degree trabecular meshwork with 40 to 60 shots. These two studies showed a mean IOP change after the second SLT was 2.2 mmHg and 4.5 mmHg at about 15 months respectively. In the studies of Khouri et al. and Francie et al., approximately 100 applications on average were performed on 360-degree trabecular meshwork in two SLT treatments, and the mean (SD) IOP reduction was 2.9 (5.8) mmHg at 12 months and 3.4 (3.6) mmHg at 6 to 12 months respectively after the repeat SLT. The wide range of mean IOP change (from 2.2 to 4.5 mmHg) among those studies may be due to different baseline characteristics of patients, such as type of glaucoma and baseline IOP. Also, a relatively large variance presented in most of the repeat SLT studies may attribute to the discrepancy of the mean values. One the one hand, the procedure itself or personal characteristics may produce a wide range of outcomes. On the other hand, the fewer shots are applied on the trabecular meshwork in each SLT, the less possible for overlap between the initial and the second applications, and the efficacy of repeat SLT possibly depends on the number of overlap laser shot.
Although the mean IOP change was significantly greater in the SLT group than the ALT group within 3 months, the equivalence of mean IOP change was seen during 3 to 12 months shown in Table 3 and Table 4 of Chapter 4. The outcomes of laser success, which was defined as an IOP reduction more than 2 mmHg from baseline, were consistent with the IOP change shown in Table 5 of Chapter 4.

The number of medication increased a little on average in both groups, while the difference at 12 months between the two groups was not significant (Table 9 in Chapter 4). One patient (2%) in the SLT group and 4 (7%) in the ALT group received either further laser trabeculoplasty or incisional glaucoma surgery during the 12-month follow-up. Neither the risk difference nor the relative risk of processing to surgery was found a significant difference (Section 4.2 in Chapter 4). Those two secondary outcomes both suggests a comparable efficacy between SLT and ALT in IOP control within 12 months.

A series of planned subgroup analyses were conducted, including POAG subgroup, and subgroups divided by age, gender, number of glaucoma risk factor, central corneal thickness (CCT) at baseline, number of glaucoma medication at baseline, PGAs users, CAIs users, and previous SLT time. All those subgroup analyses did not find a significant difference between the two laser treatments in IOP change (Table 10 in Chapter 4).

Safety
IOP spike was not detected (0%) at post-laser one hour in the Repeat Laser Study (Section 4.2 in Chapter 4). Among the previous RCTs comparing SLT and ALT, two studies did not detect an IOP spike which requires accurate surgery or an IOP increase ≥ 6 mmHg, but several studies reported an IOP spike between 4.5% to 15.4% after SLT and 3.5% to 17% after ALT. In repeat SLT studies, IOP spike was absent in several studies, or had a rate of 2.3% in one study after either the initial or the second SLT. The outcomes of those repeat SLT studies may indicate that the second SLT will not alter the possibility of IOP spike. It was found that IOP spike after laser trabeculoplasty was related to high energy level. Although IOP spike after laser trabeculoplasty is usually transient and resolve spontaneously or with glaucoma medication, IOP spike after trabeculectomy has been found to be associated with a long-
term IOP increase. Whether IOP spike predicts a worse outcome of laser trabeculoplasty needs further investigations.

Anterior chamber cell at post-laser 1 hour was mild and ranged from 0 to 2 in the SLT group and 0 to 1 in the ALT group (Section 4.2 and Table 7 in Chapter 4). However, anterior inflammation was more severe (mean anterior chamber cells 0.51 vs 0.32) and happened in more patients (74% vs 64% at one hour; 25% vs 7% at one week) within one week after SLT than ALT (Table 7 in Chapter 4). It is in line with the result reported by Damji et al., while contrary to those from some other studies. The inconsistency of the comparison of these two lasers can be explained partially by the difference of the post-laser steroid treatment schedule and the anterior chamber inflammation examination method (subjective or objective). After one month, the percentage of patients who had a clear anterior chamber was almost identical between the two groups. Besides, the percentage of a trabecular meshwork pigmentation greater than 1 grade was almost identical between baseline and 12-month follow-up in both groups (Table 8 in Chapter 4), which also suggested an absent or mild post-laser anterior chamber inflammation after SLT and ALT.

The mean best-corrected visual acuity (BCVA) did not have a change larger than 0.1 LogMAR throughout the study period in both groups (Table 6 in Chapter 4). Furthermore, the post-laser visual acuity was comparable between SLT and ALT at all the time points. Similarly, the study of Damji et al. did not find a significant change of mean BCVA during the follow-up period after SLT or ALT. It suggests that laser trabeculoplasty is safe in terms of preserving visual acuity compared with incisional glaucoma surgeries, which can cause a significant BCVA reduction after surgery.

In summary, SLT had an equivalent IOP reduction effect compared with ALT for patients who had previous 360-degree SLT. Complications after SLT or ALT were rare and mild.

**Predictors of laser success**

In this thesis, we set up a prediction model to explore the predictors at baseline for laser trabeculoplasty treatment success, which was defined as IOP decrease larger than 2 mmHg from baseline at 12 months. The covariates were selected from those correlated
with the efficacy of SLT or ALT in previous studies. We found only the IOP and the number of glaucoma medication used at baseline were significant predictors of success, while age, central corneal thickness, trabecular meshwork pigmentation, prostaglandin analogues (PGAs), and carbonic anhydrase inhibitors (CAIs) were not significantly associated with success (Table 11 in Chapter 4).

Higher baseline IOP was confirmed to be a strong predictor of treatment success at 12 months after either univariate or multivariate analysis. For every 4 mmHg elevation of baseline IOP, the odds of treatment success were expected to increase 1 time if the number of glaucoma medication was constant. The magnitude in this study is within the range of the odds ratio (1.12 to 1.58) in numerous studies, including various definitions of success and using univariate or multivariate analyses with follow-up time between 1 month to 12 months. Also, this positive association is in accordance with a number of other studies evaluating predictors of IOP-lowering effect of SLT or ALT. Since the conventional outflow pathway of aqueous humor is pressure dependent, which may explain why higher baseline IOP had a greater IOP reduction after laser trabeculoplasty.

The number of glaucoma medication was found to have a negative association with treatment success. The point estimate of odds of laser trabeculoplasty success decreased almost 40% for the addition of one glaucoma medication at baseline holding baseline IOP fixed. Similarly, Lee et al. found using 3 types of glaucoma medication suggested a higher possibility of SLT treatment failure. By contrast, some other studies did not find an association between the number of glaucoma medication at baseline and IOP reduction effect after laser trabeculoplasty.

It is possible that the association between the number of glaucoma drug and laser efficacy was confounded by indication. One of the possible confounders is the severity of glaucoma. Two studies found that pretreatment visual field defect was associated with treatment failure after ALT. However, neither retinal nerve fiber layer thickness nor visual field index, both of which can represent the stage of glaucoma in a certain degree, was found to be correlated with the IOP-lowering efficacy of SLT. Therefore,
other confounders may exist, such as the structure of trabecular meshwork, which can cause the reduction of aqueous humor outflow. However, controlling for the indications is complicated because some of those confounders are not likely to be quantified, and some of them are not available in this study.

Other reasons for the disagreement regarding the association between the number of glaucoma medication and laser treatment success among studies include differences of participant characteristics, definition of laser success, statistics method (linear regression model, logistic regression model, or ANOVA), and stopping rule of covariate selection (p value) when regression model was developed.

We did not find an association between age and laser success, while Ayala et al. detected a negative correlation between age and time to treatment failure. However, many other studies also considered that age is not a significant predictor for IOP-lowering effect of laser trabeculoplasty. The opposite conclusion may be due to the mean age (76.5 years) of the participants in the study of Ayala et al. being apparently higher than the others (57.6 to 69.08 years).

In addition, baseline CCT was not a significant predictor for laser trabeculoplasty success in our study, which is in agreement with many previous studies. In opposite to those conclusions, Shazely et al. found patients with thinner CCT had a lower percentage of IOP reduction after SLT than the thicker ones. However, the retrospective study used simply a t-test and did not adjust for IOP, which is positive correlated with the thickness of central cornea. Therefore, the predictive effect of CCT was probably confounded by baseline IOP.

Although we did not find an association between trabecular meshwork pigmentation and success, several studies found a higher grade of trabecular meshwork pigmentation had a larger IOP reduction after SLT as well as ALT. However, the former two studies did not adjust for confounders, such as baseline IOP, which may bias the outcome. Therefore, some other studies, all of which used logistic regression model analysis and adjusted for potential confounders, drew the same conclusion as ours.
Nevertheless, since most of the studies investigated only SLT, the association between trabecular meshwork pigmentation and ALT treatment efficacy need further evaluations.

Neither PGAs nor CAIs were found correlated to the treatment success in this thesis, which is consistent with the conclusions from other studies.\textsuperscript{122 123 126 132 135 137 147 148 162} By contrast, some other studies found a positive or negative association between PGAs and IOP-lowering effect of SLT.\textsuperscript{124 128 133 159 160} Whereas this thesis included both SLT and ALT patients in the regression model, all those studies evaluated the association between PGAs and SLT only. Besides, the statistical method and covariates included in the regression model are different from ours. Similarly, two studies found a significant association between CAIs and efficacy of SLT.\textsuperscript{158 161} However, the follow-up period (one was 5 years and the other was 1 month) has a huge difference from ours.

In summary, pre-laser IOP has been found again as the strong predictor of treatment success in this thesis. Although the number of glaucoma drug at baseline was found negative correlate with success, the association may be due to confounding by indication, and the conclusions varied among studies. Therefore, this relationship needs further investigation.

5.2 Strengths of the study

There are some apparent strengths of this study. First, the data were obtained from an ongoing study which was the first registered study comparing SLT and ALT for those who had previous 360-degree SLT. The study is a randomised controlled trial, which is an optimal design for controlling confounders.

Second, the participants were recruited from seven cities covering a large geographical area across Canada, which provided a generalizable sample of the study. In addition, all the physicians are specialists to ensure an adequate surgical skill. Furthermore, the laser procedure was standardised in the study protocol. Therefore, the treatment effect was expected to be consistent across different surgeons. The two features of the study helped increase the external and internal validity of the outcomes.
Third, attributed to the double entry procedure, the digital data were reliable since the missing value and error rates were low (0.3% and 0.7% respectively) after the comparison with the paper records (Appendix 1A and 1B in Chapter 3).

Fourth, the rate of withdrawal or lost to follow-up was low with 7 in 128 patients (5%), and it was almost balanced in the two treatment groups with 4 (6%) in the SLT group and 3 (5%) in the ALT group (Figure 2 in Chapter 4). It ensured the validity of the outcome analyses.\textsuperscript{179}

Fifth, we found an equivalent IOP-lowering effect at 12 months between SLT and ALT even for those who had received 360-degree SLT before. The equivalence was confirmed for both complete cases or per-protocol patients. These outcomes provide a useful evidence for clinical decision makes.

Sixth, we found a significant correlation between IOP or number of glaucoma medication at baseline and the efficacy of laser trabeculoplasty ($p = 0.01$ and $0.03$ respectively) (Table 11 in Chapter 4). It also provides a meaningful implication for clinical practice.

\section*{5.3 Limitations of the study}

\textbf{Evaluating equivalence}

First, the sample size was 115, which represented only 84\% information of all the 137 randomised patients. However, after the extreme case analyses, the difference of IOP reduction between the two laser groups was found not significant, which indicates that the equivalent result is robust.

Second, we found that some of the patients who had a glaucoma surgery during the follow-up period dropped out from the study while some remained in the study. Besides, we excluded some of the patients who had missing values for secondary outcomes in the complete case analysis. Those may cause some unbalance between the two intervention groups and bias the outcomes.

Third, over 80\% of the participants were Caucasian, which may limit the generalization of the conclusion to other ethnicity groups.
Fourth, although confidence interval approach is informative for testing equivalence, it cannot provide a p-value, which is used to determine the strength of evidence to reject the null hypothesis.\(^{180}\)

**Prediction model**

First, we did not explore all the potential predictors in the original regression model. Aqueous humor dynamics, maximum pre-SLT IOP, visual field defect, and diabetes have been shown to be significant predictors of laser treatment in some previous studies.\(^{134}\)\(^{138}\)\(^{139}\)\(^{142}\)\(^{147}\)\(^{148}\) It was because the data of those variables were not recorded or not complete in the Repeat Laser Study.

Second, the backward stepwise method for selecting variables in the prediction model has disadvantages, since stepwise methods are known to have some drawbacks. They include unstable selection, coefficient estimation bias, misspecification of variability, and possible to create a lesser predictive model than a full model.\(^{169}\)

Third, the area under the receiver-operating characteristic curve (AUC) of the prediction model for treatment success was 0.68, which suggested the final model was only modestly successful in discriminating between the patients who will succeed and those who will not succeed.\(^{181}\) In the study of Martow et al.,\(^{131}\) the authors included gender, baseline IOP, maximum IOP, previous ALT, trabecular meshwork pigmentation, and type of baseline glaucoma eye drop in the multivariate analysis to predict SLT treatment success. Baseline IOP was the only significant predictor \((p < 0.05)\) which was kept in the model. The AUC of the model was 0.797. Mao et al.\(^{134}\) also performed a multivariate analysis with baseline IOP, maximum pre-SLT IOP, trabecular meshwork pigmentation, washout of eye drops, and gender as candidate predictors. Both baseline IOP and maximum pre-SLT IOP were the significant predictors \((p < 0.0001\) and \(p = 0.022)\) and were kept in the model which produced an AUC of 0.72. Those two studies evaluated the predictors for the efficacy of primary SLT and produced a larger AUC than ours. It may indicate that the efficacy of primary laser treatment is more predictable than repeat laser treatment. In addition, the study of Mao et al. suggests that including maximum pre-
treatment IOP may increase the discrimination ability of the model. However, maximum pre-treatment IOP was not documented in the Repeat Laser Study.

Though some drawbacks were identified in the creation of the prediction model, we have to repeat that the primary objective of the Repeat Laser Study and this thesis was to confirm the hypothesis that SLT and ALT have an equivalent IOP-lowering efficacy even after 360-degree SLT. The sample size and data were determined and recorded based on the primary objective. We created a prediction model to explore possible predictors for treatment success for this particular group of patients. The significant correlation between baseline IOP or number of medications used at baseline and treatment efficacy was identified after adjusting for most of the important potential confounders. Therefore, the objective of the creation of the prediction model to explore the predictors for the IOP-lowering effect of laser trabeculoplasty has been achieved.

5.4 Conclusions and implications

The industry claims that SLT is repeatable because it does not cause any mechanical change of the targeted tissue (mainly refers to the trabecular meshwork). However, the evidence of the repeatability of SLT is scant.

In our study, either SLT or ALT after previous 360-degree SLT had a less than 70% of the IOP reduction caused by the initial SLT or ALT when the outcomes were compared with other studies. This lowered efficiency was also seen in some studies which compared the difference between the primary and repeat SLT, although a significant difference was not found in these studies. The different efficacy between the primary and repeat laser treatment suggests some irreversible changes of SLT-targeted tissue may happen, and those changes can alter the efficacy of the next SLT or ALT.

Another possibility is that the difference between the primary and repeat laser is owing to confounding by indications. For example, the bio-characteristics of the people who failed for the primary SLT and those who can maintain a target IOP after the primary SLT may be different. Some other confounders such as surgical skill of physicians, demographic
characteristics of the patients, etc. can also lead to different outcomes between ours and others.

In addition, a less efficacy of the secondary SLT than the primary SLT suggests that the degree of IOP reduction of the third or more SLT will likely be even less beneficial. The open-label ongoing study described in Section 5.5 will answer this question.

The IOP lowering-effect of 180-degree SLT was equivalent to 180-degree ALT in those who had 360-degree SLT before. The difference of mean IOP reduction between the two treatment groups was -0.01 mmHg (95% CI, -1.86 to 1.84; p = 0.99). Also, the percentage of IOP spike at one hour was 0% after the two laser treatments. The difference of mean BCVA at 12 months was not significant with p = 0.09. The difference of percentage of patients who were free of anterior chamber inflammation at 12 months was almost comparable (RD, -0.02 and p = 0.55; RR, 0.98 and p = 0.55). Since the efficacy and safety of the two lasers were comparable, when people need a further intervention, some other issues can be considered such as the cost, surgical skill, post-laser feelings, etc.

Regarding the predictors of the efficacy of the laser trabeculoplasty, baseline IOP and number of glaucoma medication were two significant predictors for the success of laser trabeculoplasty (p = 0.01 and p = 0.03). It suggests that patients who are on maximal tolerated medical therapy may not be suitable for laser trabeculoplasty as the next step for IOP control, and an incisional surgery should be applied instead.

5.5 Future studies
Based on the outcomes of this thesis, some extensions or improvement of the study could be considered in the future studies: First, an extension study of the Repeat Laser Study is being carried out. It will extend the follow-up time up to 3 years after the laser treatment. During the observation period, if the IOP is not controlled under the target level, patients will be treated with repeat SLT, another medication, or glaucoma surgery after the discussion of the patients and the physicians. In the extension study, on the one hand, the long-term comparison between SLT and ALT can be observed. On the other hand, it provides an opportunity to evaluate the efficacy of the third or more repeat SLT. Second, studies can be designed to evaluate the effect specifically on non-Caucasian. Third, future
studies can try to use different predictor selection methods (e.g., Bayesian model average, shrinkage of regression coefficients to zero, etc.) and compare the performance of those prediction models.
References


82. Waisbourd, M. & Katz, L. J. Selective laser trabeculoplasty as a first-line therapy:


96. National Collaborating Centre for Acute Care. *Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension.* (the
National Collaborating Centre for Acute Care at The Royal College of Surgeons of England, 2009).


Appendices

Appendix 1A: Errors and missing values found by comparing web-based data and paper records for 14 samples available in the Ivey Hospital in June 2017

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<td>Web (paper)</td>
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Appendix 1B: Errors and missing values after comparing web-based data and paper records for 14 samples available in Ivey hospital in June 2017

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<td>Web (paper)</td>
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<td>Visit 5: 20/20 (20/20-2)</td>
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<td>Altace: Missing (11); Hydrochlorothiazide: Missing (11); Zyloprim: Missing (11)</td>
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### Appendix 2A: Actions for errors and missing values of 137 patients who were recruited in the study and documented by June 2017

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Appendix 2B: Actions for errors and missing values of 137 patients who were recruited in the study and documented by June 2017

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<td>modification</td>
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<td>original</td>
</tr>
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Appendix 2C: Actions for errors and missing values of 137 patients who were recruited in the study and documented by June 2017

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### Appendix 3: Number of errors and missing values found by June 2017 in the digital data sets of 137 patients

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<td>IOP &gt; 16 mmHg in two consecutive visit separated at least one month</td>
<td>14 (10%)</td>
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<tr>
<td>BCVA &gt; 20/200 for two eyes</td>
<td>1 (0.7%)</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria (n=137)</th>
<th>Number of patients who violated exclusion criteria (%)</th>
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<td>Corneal disease</td>
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</tr>
<tr>
<td>Systematic or topical steroids used at baseline</td>
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</tr>
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<td>Systematic steroids anticipated in the 6 months following treatment</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Logic and consistency check (n=137)</th>
<th>Number of inconsistent records (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riskfactor (age &gt; 60)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Riskfactors (not Caucasian)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>IOP 1-hour follow-up time earlier than laser treatment time</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

| Error or missing in medication records                                                    | N (%)                                               |
| Ocular medications labeled as non-ocular medications (n=414 records)                    | 5 (1%)                                               |
| Missing start year (non-ocular medication) (n=382 records)                               | 4 (1%)                                               |
| Missing start month (non-ocular medication) (n=382 records)                              | 146 (38%)                                            |
| Missing stop month when stop year is not missing (non-ocular medication) (n=382 records)| 1 (0.3%)                                              |
| Missing start year (ocular medication) (n=414 records)                                   | 6 (1%)                                               |
| Missing start month (ocular medication) (n=414 records)                                  | 20 (5%)                                              |
| Missing stop month when stop year is not missing (ocular medication) (n=414 records)     | 3 (0.7%)                                              |

| Missing of laser treatment time (n=137)                                                   | 16 (12%)                                             |
Curriculum Vitae

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Post-secondary Education and Degrees:
- Sun Yat-sen University
  Guangzhou, Guangdong, China
  1998-2003 B.A.
- Sun Yat-sen University
  Guangzhou, Guangdong, China
  2006-2009 M.A.
- The University of Western Ontario
  London, Ontario, Canada
  2015--2018 M.A. Candidate

Honours and Awards:
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  2015-2017
- Canadian Society For Epidemiology And Biostatistics (CSEB) 2017 Biennial Conference Travel Award


Presentation (2015-2017):