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Primary Selective Laser Trabeculoplasty for Open-Angle Glaucoma and Ocular Hypertension

Clinical Outcomes, Predictors of Success, and Safety from the Laser in Glaucoma and Ocular Hypertension Trial

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Purpose: To report clinical efficacy, predictors of success, and safety of primary selective laser trabeculoplasty (SLT) used in treatment-naive patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Design: Post hoc analysis of a multicenter, prospective, randomized, controlled trial.

Participants: Treatment-naive patients with OAG or OHT.

Methods: Patients randomized to SLT or topical medication and treated to predefined target intraocular pressures (IOPs) requiring ≥20% IOP reduction from baseline for all disease severity levels.

Outcome Measures: Initial (early) absolute IOP-lowering at 2 months. Achievement of drop-free disease-control: meeting target IOP without disease progression or need for additional topical medication over 36 months after SLT. Predictors of early absolute IOP-lowering and drop-free disease-control after single initial SLT. Frequency of laser-related complications.

Results: A total of 611 eyes (195 OHT and 416 OAG) of 355 patients received SLT, and 622 eyes (185 OHT and 437 OAG) of 362 patients received topical medication at baseline. Early absolute IOP-lowering after SLT was no different between OHT and OAG eyes (adjusted mean difference = −0.05 mmHg; 95% confidence interval [CI], −0.6 to 0.5 mmHg; $P = 0.85$). No difference was noted in early absolute IOP-lowering between topical medication and primary SLT (adjusted mean difference = −0.1 mmHg; 95% CI, −0.6 to 0.4 mmHg; $P = 0.67$). Early absolute IOP-lowering with primary SLT was positively associated with baseline IOP (coefficient 0.58; 95% CI, 0.53−0.63; $P < 0.001$) and negatively with female gender (coefficient −0.63; 95% CI, −1.23 to −0.02; $P = 0.04$). At 36 months, 536 eyes (87.7% of 611 eyes) of 314 patients (88.5% of 355 patients) were available for analysis. Some 74.6% of eyes (400 eyes) treated with primary SLT achieved drop-free disease-control at 36 months; 58.2% (312 eyes) after single SLT. Total SLT power and 2-month IOP were predictors of drop-free disease-control at 36 months after single SLT. Six eyes of 6 patients experienced immediate post-laser IOP spike (>5 mmHg from pretreatment IOP) with 1 eye requiring treatment.

Conclusions: Primary SLT achieved comparable early absolute IOP-lowering in OHT versus OAG eyes. Drop-free disease-control was achieved in approximately 75% eyes at 36 months after 1 or 2 SLTs, the majority of these after single SLT. These analyses are exploratory but support primary SLT to be effective and safe in treatment-naive OAG and OHT eyes. *Ophthalmology 2019;126:1238-1248 Crown Copyright © 2019 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Over the past 2 decades, selective laser trabeculoplasty (SLT) has become an established treatment to lower intraocular pressure (IOP) for open-angle glaucoma (OAG) and ocular hypertension (OHT). Introduced by Latina and Park in 1995, SLT uses a 532 nm Q switched, frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser that delivers a short pulse duration (3 ns)[1] to reduce IOP by increasing aqueous outflow through the trabecular meshwork (TM).[2] The procedure is short and outpatient-based, with quick recovery and good safety profile.[3]

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Table 1. Severity Criteria for Setting Treatment Target Intraocular Pressure from the "Canadian Target IOP Workshop" (with Central Field Criteria Defined According to Mills)

Severity	Definition of Severity for Treatment Target IOP				
	Optic Nerve		*VF MD*		*Central (10°) Scotoma on VF*
OHT	Healthy		Any		No GON-related VFL
Mild OAG	GON	+	>−6 dB	+	None
Moderate OAG	GON	+	−6 dB< and >−12 dB	or	At least 1 central 5° point <15 dB but none <0 dB and only 1 hemifield with central point <15 dB
Severe OAG	GON	+	<−12 dB	or	Any central 5° point with sensitivity <0 dB Both hemifields contain point(s) <15 dB within 5° of fixation

dB = decibels; IOP = intraocular pressure; GON = glaucoma optic neuropathy; OAG = open-angle glaucoma; VF = visual field; VFL = visual field loss; VF MD = visual field mean deviation.

Selective laser trabeculoplasty has the potential advantage of avoiding issues associated with topical IOP-lowering medications, such as local and systemic side effects and variable patient adherence. Since Food and Drug Administration approval in 2001, SLT increasingly has been adopted into practice. In the United States, 75 647 trabeculoplasties were performed in 2001, and this increased to 142 682 procedures in 2012.[4]

Studies investigating SLT as a primary treatment have found a similar IOP-lowering efficacy and success rate to topical medication using various success criteria.[3] However, several of these studies include patients taking IOP-lowering topical medications that were stopped for a variable duration before receiving SLT.[5-8] Despite a washout period to mitigate against residual effects of prior topical treatment, SLT can be less effective after topical treatment.[6] Few studies have evaluated primary SLT in true treatment-naive patients,[9-11] and there is limited knowledge of predictors of IOP-lowering response, treatment success, and safety in such patients.

The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial was a multicenter randomized controlled trial (RCT) conducted to establish whether initial treatment with SLT is superior to initial treatment with medication for treatment-naive patients with OAG or OHT in relation to health-related quality of life (HRQL), cost-effectiveness, and clinical efficacy at 36 months.[12] Eyes in the primary SLT arm were at target IOP over more clinical visits during 36-month follow-up compared with drops, with fewer eyes demonstrating disease progression and fewer cataract and trabeculectomy surgeries. Primary SLT was found to be more cost-effective than initial medication over the course of 36 months, despite a lack of HRQL differences between the 2 arms.[13]

This report characterizes the IOP-lowering, drop-free disease-control and safety achieved by primary SLT in treatment-naive patients with OAG and OHT as part of LiGHT, in which eyes were treated to predefined target IOP on the basis of disease severity. We also investigated predictors of initial (early) IOP lowering and predictors for achieving drop-free disease-control at 36 months after single initial SLT. We hypothesized that primary SLT would demonstrate effective IOP lowering in treatment-naive OHT and OAG eyes with a comparable effect to topical medication. We anticipated that absolute IOP lowering could be greater in OHT versus OAG eyes because of higher pretreatment baseline IOPs and that drop-free disease-control would be more readily achieved in eyes with less-advanced disease because target IOPs were higher.

Methods

The study was conducted in accordance to Good Clinical Practice guidelines and adhered to the tenets of the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval was obtained. All patients provided written informed consent before participation in the trial. The LiGHT Trial is registered at www.controlled-trials.com (registration number ISRCTN32038223).

This study was a post hoc analysis of the LiGHT trial, the design and baseline characteristics of which have been described.[12,14] Briefly, consecutive eligible patients were identified at the clinics of 6 participating centers in the United Kingdom from October 2012 to October 2014. Eligible patients had newly diagnosed, untreated OAG or OHT in 1 or both eyes and qualified for treatment according to National Institute of Clinical Excellence guidelines,[15] open angles on gonioscopy, visual field loss with mean deviation (VF MD) not worse than −12 decibels (dB) in the better eye or −15 dB in the worse eye, and, for OAG, corresponding damage to the optic nerve head. Patients were 18 years or older and able to read and understand English and had a visual acuity of 20/120 or better in the treated eye(s)

Table 2. Setting Treatment Target Intraocular Pressure

Baseline Disease Severity	Treatment Target IOP
OHT	>20% IOP reduction from baseline IOP or IOP <25 mmHg (whichever lower)
Mild OAG	>20% IOP reduction from baseline IOP or IOP <21 mmHg (whichever lower)
Moderate OAG	>30% IOP reduction from baseline IOP or IOP <18 mmHg (whichever lower)
Severe OAG	>30% IOP reduction from baseline IOP or IOP <15 mmHg (whichever lower)

IOP = intraocular pressure; OAG = open-angle glaucoma; OHT = ocular hypertension.

Table 3. Baseline Characteristics of Primary Selective Laser Trabeculoplasty Arm

Characteristics	Value
Age (yrs), mean (SD)	63.4 (12.1)
Gender (patients), (%)	
Male	199 (56.1%)
Female	156 (43.9%)
Race/ethnicity (patients), (%)	
White European	242 (68.2%)
Black	77 (21.7%)
Asian	23 (6.5%)
Other	13 (3.7%)
Laterality (patients), (%)	
Bilateral eyes	256 (72.1%)
Right eye	49 (13.8%)
Left eye	50 (14.1%)
Hypertension (patients), (%)	
Yes	131 (36.9%)
No	224 (63.1%)
Diabetes mellitus (patients), (%)	
Yes	41 (11.6%)
No	314 (88.5%)
Disease severity (eyes), (%)	
OHT	195 (31.9%)
Mild OAG	309 (50.6%)
Moderate OAG	67 (11.0%)
Severe OAG	40 (6.5%)
Mean deviation (dB), mean (SD)	−3.0 (3.4)
Pattern SD (dB), mean (SD)	3.7 (2.9)
Mean HRT area (mm^2), mean (SD)	1.2 (0.4)
Baseline IOP (mmHg), mean (SD)	
Overall	24.5 (5.2)
OHT	26.5 (3.5)
OAG	23.5 (5.6)
Average trabecular pigmentation grade (eyes), (%)	
0- None	243 (39.8%)
1- Mild	264 (43.2%)
2- Moderate	101 (16.5%)
3- Dense	1 (0.2%)
Unknown	2 (0.4%)
Habitual VA (logMAR), mean (SD)	0.10 (0.2)
CCT (μm), mean (SD)	550.6 (38.1)
PXF (eyes), (%)	
Yes	5 (0.8%)
No	606 (99.2%)
Target IOP (mmHg)	
OHT	21.1 (2.4)
Mild OAG	17.9 (3.1)
Moderate OAG	15.9 (2.6)
Severe OAG	13.9 (1.6)

CCT = central corneal thickness; dB = decibels; HRT = Heidelberg Retina Tomography; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; OAG = open-angle glaucoma; OHT = ocular hypertension; PXF = pseudoexfoliation; SD = standard deviation; VA = visual acuity. Self-defined ethnicity; Asian ethnicity refers to Indian, Pakistani, Bangladeshi, and any other Asian background, black ethnicity refers to Caribbean, African, and any other black background, Other ethnicity refers to Chinese and any other ethnic groups.

and no previous intraocular surgery, except uncomplicated phacoemulsification at least 1 year before entering the trial. Patients were excluded if there were any contraindications to SLT, they were unable to use topical medical therapy, they had visually symptomatic cataract and wanted to undergo cataract surgery, or they were receiving active treatment for another ophthalmic condition. Patients with 1 or both eyes eligible were treated. All measurements influencing treatment escalation decisions—automated visual field using Humphrey Field Analyzer Mark II Swedish interactive threshold algorithm standard 24-2 program (Carl Zeiss Meditec, Dublin, CA), Heidelberg Retina Tomography disc imaging (Heidelberg Engineering, Heidelberg, Germany), and IOP (Goldmann applanation tonometry with daily calibration verification)—were performed by masked observers. Patients were monitored for 3 years. Disease category and severity were defined using preset objective severity criteria from the Canadian Target IOP Workshop[16] with additional central VF loss criteria[17] (Table 1).

Severity stratification (OHT, mild, moderate, or severe OAG) determined an eye-specific "Target IOP" and follow-up intervals. Target IOP was objectively defined using both percentage reduction from untreated IOP and an absolute value, with the final target IOP being the lower of the 2 values (Table 2). Achievement of target IOP thus required a minimum IOP reduction of >20% from baseline IOP, irrespective of disease severity.

Standardized criteria to escalate treatment were used according to a protocol following international guidelines by the European Glaucoma Society,[18] American Academy of Ophthalmology Preferred Practice Pattern,[19] and the South-East Asia Glaucoma Interest Group.[20] These were incorporated into a real-time web-based clinical decision support software, based on optic disc analysis (Heidelberg Retina Tomography), automated visual fields analysis (Humphrey Visual Field) and IOP measurements. Criteria for defining IOP not at target and disease progression by Heidelberg Retina Tomography and VF have been reported.[12]

Standardization of SLT delivery was achieved by protocol-defined settings and clinical end points. The protocol advised 360-degree TM treatment, 100 nonoverlapping shots (25 per quadrant) of a preset 3 nanoseconds duration and preset 400 μm spot size, with the laser energy varied from 0.3 to 1.9 mJ by the clinician according to just observable bubble formation. Intraocular pressure was checked 60 minutes after SLT procedure. One SLT re-treatment was permitted during the study, if/when a treatment escalation was recommended by the decision support software and confirmed by the treating clinician. To allow time for the full effects of laser to occur, the earliest interval at which repeat SLT was permitted was after the first scheduled visit 2 months after initial SLT. Selective laser trabeculoplasty was not repeated if significant complications of laser treatment occurred, if there was a lack of IOP-lowering response after initial SLT (judged by the treating clinician − not protocol defined), or if other new medical conditions prevented repetition. In such cases, treatment escalation with topical medication rather than repeat SLT was permitted. In eyes that underwent repeat SLT, if further treatment escalation was required, the next step was topical medication. The earliest planned interval at which this could be initiated was after the first scheduled visit 2 months after repeat SLT.

Follow-up intervals were initially set at entry to the study according to National Institute of Clinical Excellence guidance[21] and subsequently adjusted on the basis of IOP control, glaucoma progression, or adverse reactions. The routine schedule of appointments and assessments for patients has been published previously.[14] At follow-up, patients underwent visual acuity testing (Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution), slit-lamp examination, visual field testing (Humphrey Field Analyzer Mark II SITA standard 24-2), Heidelberg Retina Tomography optic disc imaging, IOP measurement (Goldmann applanation tonometry), and clinical assessment of the optic discs, maculae, and fundi.

To investigate the IOP-lowering efficacy of primary SLT for OHT versus OAG, we evaluated the initial (early) absolute IOP reduction at 2 months for all eyes receiving primary SLT. This was the first scheduled visit (after safety IOP check visit at 2 weeks

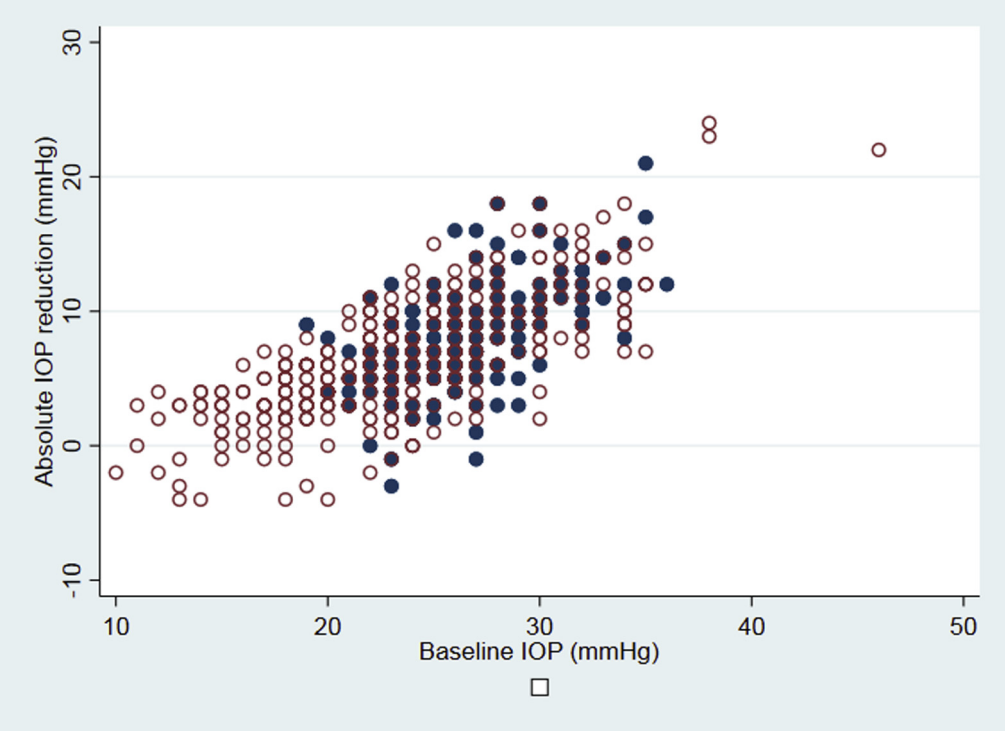

Figure 1. Scatter plot of absolute intraocular pressure (IOP) reduction versus baseline IOP in all eyes (559 eyes) at 2 months after initial SLT. Filled circles: ocular hypertension (OHT). Hollow circles: open-angle glaucoma (OAG).

post-laser) after laser at baseline. To contextualize the early IOP-lowering efficacy of primary SLT in treatment-naive eyes, we compared early absolute IOP reduction at 2 months after primary SLT with 2-month absolute IOP reduction in eyes from the Medication-1st arm of the LiGHT trial that had commenced topical medication at baseline. To investigate if early absolute IOP lowering after primary SLT was predicted by clinically relevant baseline factors, a linear regression analysis was performed (see "Statistical Methods").

The LiGHT trial followed a "Treat in Pursuit of Control" design, and thus, after the first scheduled visit at 2 months, the web-based clinical decision support software began to monitor and escalate treatment (if required) for each eye based on achievement of disease control, that is, achievement of predefined target IOP with no objective evidence of disease progression. Eyes with OAG had lower predefined target IOPs than OHT eyes (Table 2) and thus were more likely to require greater treatment intensity compared with OHT eyes to achieve disease control. Intraocular pressure comparisons between OHT and OAG eyes at later time points would be confounded by differences in treatment intensity and were not performed.

We evaluated treatment intensity of primary SLT in OHT versus OAG eyes by assessment of drop-free disease-control achieved by primary SLT at 12, 24, and 36 months. The LiGHT treatment protocol permitted a single SLT retreatment (if required); therefore, we determined drop-free disease-control achieved by 1 or 2 SLTs collectively and by initial, single SLT alone.

In the SLT literature, the most commonly defined measure of success is a minimum IOP reduction of ≥20% from baseline IOP after SLT at a specified time point, without the need for further intervention.[22] In LiGHT, the predefined target IOPs required a minimum IOP reduction of >20% from baseline IOP for all disease severities (Table 2); thus, eyes achieving drop-free disease-control at 36 months after a single, initial SLT would serve as a useful (although more stringent) success comparator with preexisting SLT studies. A logistic regression analysis of factors to predict eyes achieving drop-free disease-control at 36 months after initial, single SLT was performed. To determine the safety of primary SLT, the frequency of laser-related complications and adverse events over 36 months was collated.

Statistical Methods

The sample size for LiGHT was based on analyses planned to assess HRQL in treatment-naive patients with OAG/OHT treated initially with primary SLT or topical medication. The sample size was 718 patients, calculated to detect a difference of 0.05 in EQ-5D-5L between the 2 arms at 36 months using a 2-sample *t* test at the 5% significance level with 90% power, assuming a common standard deviation (SD) of 0.19[23] and 15% attrition.

In this report, the unit of analysis was the eye. All eligible study eyes that received SLT at baseline were included in the analysis with appropriate measures taken to account for correlation among paired eyes within a subject.

Summary statistics of the demographic and clinical characteristics are presented for all eligible study eyes. Descriptive statistics are presented as means and SDs. Analysis comparing baseline demographics of eyes available to those unavailable to analyze at 36 months was performed. The *t* test or Wilcoxon rank-sum test was used for comparison of continuous data, and chi-square test was used for categoric data.

To compare absolute IOP reduction at 2 months between OHT and OAG eyes, a mixed-effects model using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes was performed. The model also

Table 4. Univariable Linear Regression Analysis for Absolute Intraocular Pressure Reduction

Variable	Coefficient	95% CI	P Value
Baseline IOP (mmHg)	0.59	(0.54–0.64)	<0.001*
Race/ethnicity			0.17
Black	1.18	(0.08–2.29)	
Asian	0.89	(−0.87 to 2.66)	
Other	0.70	(−1.75 to 3.15)	
*Reference white European			
Sex			
Female	−1.42	(−2.29 to −0.54)	0.002*
Age (yrs)	−0.04	(−0.08 to 0.00)	0.05*
CCT (μm)	0.01	(0.00–0.02)	0.15
PXF (Y/N)			
No	−1.62	(−4.94 to 1.69)	0.34
Average TM Pigmentation grade			0.12
1- Mild	−0.12	(−1.04 to 0.81)	
2- Moderate	0.03	(−1.16 to 1.23)	
3- Dense	6.51	(1.06–12.0)	
*Reference no pigmentation			
Phakic status (Y/N)			
Phakic	0.70	(−0.90 to 2.29)	0.39
Hypertension (Y/N)			
No	0.05	(−0.87 to 0.96)	0.92
Diabetes mellitus (Y/N)			
No	0.82	(−0.51 to 2.15)	0.22
Total power 1st SLT (mJ)	0.01	(−0.01 to 0.03)	0.29
Total No. of shots 1st SLT (shots)	0.04	(−0.03 to 0.11)	0.26

CCT = central corneal thickness; CI = confidence interval; IOP = intraocular pressure; PXF = pseudoexfoliation; SLT = selective laser trabeculoplasty; TM = trabecular meshwork.
*Covariates that achieved $P < 0.10$ in the initial variable selection linear regression analyses were baseline IOP ($P < 0.001$), gender ($P = 0.002$), and age ($P = 0.05$).

controlled for pretreatment baseline IOP and treating center (to control for center effects in a multicenter trial). To compare absolute IOP reduction at 2 months between primary SLT versus topical medication, a similar mixed-effects model was also used.

To examine baseline predictors of early absolute IOP reduction at 2 months in eyes receiving primary SLT, univariate mixed effect linear regression analyses were performed using the eye as the unit of analysis and using patients as a random factor to adjust for correlation between paired eyes. Patient-related baseline characteristics considered for univariable selection were age, gender, ethnicity, phakic status, baseline IOP, central corneal thickness, TM pigmentation, pseudoexfoliation, hypertension, and diabetes mellitus. Laser-related characteristics included total SLT power and total number of SLT shots of initial SLT at baseline.

Table 5. Multivariable Linear Regression Analysis for Absolute Intraocular Pressure Reduction

Variable	Coefficient	95% CI	P Value
Baseline IOP (mmHg)	0.58	(0.53–0.63)	<0.001
Sex	−0.63	(−1.23 to −0.02)	0.04
Female			

CI = confidence in interval; IOP = intraocular pressure.

Covariates that achieved $P < 0.10$ in the univariable selection regression analyses were entered in a mixed-effect multivariable linear regression model controlling for LiGHT stratification factors (disease severity and treating center). The regression model was then run, with nonsignificant variables removed one by one until only significant ($P < 0.05$) variables remained.

A similar approach involving logistic regression was used to look for predictors of drop-free disease-control at 36 months. For the logistic regression analysis, a success criterion defined as eyes that achieved drop-free disease-control after initial, single SLT at baseline was used. This was a more stringent criterion than used elsewhere. We also considered the 2-month IOP to assess if this was a posttreatment predictor of drop-free disease-control at 36 months.

Statistical significance was defined as a 2-sided P value < 0.05. Analyses were carried out using Stata15 (Stata Statistical Software: Release 15, 2015; StataCorp LP, College Station, TX).

Results

A total of 356 patients (613 eyes) were randomized to the Laser 1st arm of LiGHT. One patient (2 eyes) withdrew consent before receiving SLT at the baseline visit; thus, 355 patients (611 eyes) received primary SLT. At 36 months, 536 eyes of 314 patients were available for analysis. Of the 75 remaining eyes, 22 eyes (of 13 patients) were formally lost to follow-up (withdrew, died, illness, or moved) during the course of the 3-year trial. The remaining 53 eyes (of 28 patients) were still returning HRQL questionnaires in the main LiGHT study, but clinical data were not available at the 36-month time-point. Analysis comparing baseline demographics of eyes available versus unavailable to analyze at 36 months (536 vs. 77 eyes) demonstrated no clinically or statistically significant differences in age, baseline IOP, ethnicity, gender, disease severity, and VF mean deviation. A statistically but not clinically significant difference in baseline visual acuity was noted between groups (mean difference logarithm of the minimum angle of resolution −0.06; 95% CI, −0.1 to −0.01; $P = 0.02$) (Appendix 2, available at www.aaojournal.org).

Baseline Characteristics

Baseline demographic data of the 611 eyes are shown in Table 3. There was a greater proportion of male patients than female patients (56.1% vs. 43.9%) at baseline. The most common ethnicities were white European (68.2%) and black (21.7%). Some 72.1% of patients had both eyes in the study, 13.8% had only the right eye, and 14.1% had only the left eye in the study; 31.9% of eyes had a diagnosis of OHT (195 eyes) compared with 68.1% of eyes with OAG (416 eyes). This is reflected in the average mean deviation (MD) value of −3.0 dB. Mean baseline IOP was 24.5 mmHg (SD, 5.2) for all eyes but was greater in OHT eyes (26.5 mmHg; SD, 3.5) than in OAG eyes (23.5 mmHg; SD, 5.6). During initial SLT, mean total power delivered was 90.4 (SD, 23.5) mJ via a mean treatment of 99.2 (SD, 5.1) shots. Baseline demographic data of the 622 eyes in the Medication 1st arm is also provided (Appendix 3, available at www.aaojournal.org).

Early Intraocular Pressure–Lowering Efficacy of Primary Selective Laser Trabeculoplasty

A total of 559 eyes (of 611 eyes at baseline) were available for analysis at the 2-month time point in the primary SLT arm having undergone initial SLT at baseline (Fig 1). Mean initial IOP lowering at 2 months was 8 mmHg (SD, 4.0) in OHT eyes and 6.5 mmHg (SD, 4.3) in OAG eyes. Mean percentage IOP

Table 6. Eyes Achieving Drop-free Disease-Control Using 1 or 2 Selective Laser Trabeculoplasties

Disease Severity	12 mos Total Eyes Available for Analysis (n)	12 mos Eyes Achieving Drop-free Disease Control % (n)	24 mos Total Eyes Available for Analysis (n)	24 mos Eyes Achieving Drop-free Disease Control % (n)	36 mos Total Eyes Available for Analysis (n)	36 mos Eyes Achieving Drop-Free Disease Control % (n)
All eyes	608	85.2% (518)	576	79.2% (456)	536	74.6% (400)*
OHT	192	92.7% (178)	174	92% (160)	158	88.6% (140)
Mild OAG	315	87.3% (275)	293	81.2% (238)	269	76.6% (206)
Moderate OAG	54	63% (34)	69	56.5% (39)	57	56.1% (32)
Severe OAG	47	65.9% (31)	40	47.5% (19)	52	42.3% (22)

OAG = open-angle glaucoma; OHT = ocular hypertension.
*One eye was protocol deviation and received 3 selective laser trabeculoplasties.

reduction was 29.7% (SD, 13.1) in OHT eyes and 26.1% (SD, 14.7) in OAG eyes, respectively. A clear trend was noted toward increasing absolute IOP reduction with higher baseline IOP in both OHT and OAG eyes (Fig 1), but there was no significant difference in early absolute IOP lowering between OHT and OAG eyes having controlled for pretreatment baseline IOP and center effects (adjusted mean difference = −0.05 mmHg; 95% confidence interval [CI], −0.6 to 0.5 mmHg; $P = 0.85$).

For comparison, 594 eyes (of 622 eyes at baseline) were available for analysis in the Medication 1st arm at 2 months. Of these, 99.3% (590 eyes) were receiving a single medication (96.1% were receiving topical prostaglandin, 1.9% were receiving a β-blocker, 0.3% were receiving a carbonic anhydrase inhibitor, 0.3% were receiving an alpha agonist, and 0.7% were receiving 2 medications). Mean initial IOP lowering at 2 months was 7.6 mmHg (SD, 4) in OHT eyes and 6.8 mmHg (SD, 4.4) in OAG eyes. Mean (SD) percentage IOP reduction was 27.9% (13.5) in OHT eyes and 27.9% (14.4) in OAG eyes, respectively.

Overall, absolute IOP reduction at 2 months was no different between topical medication and primary SLT (adjusted mean difference = −0.1 mmHg; CI, −0.6 to 0.4 mmHg; $P = 0.67$). There was no difference in absolute IOP reduction for OHT eyes (adjusted mean difference = 0.4 mmHg; CI, −0.4 to 1.2 mmHg; $P = 0.31$) or OAG eyes (adjusted mean difference = −0.2 mmHg; CI, −0.8 to 0.3 mmHg; $P = 0.36$) between the 2 treatment groups.

Predictors of Early Intraocular Pressure–Lowering Response after Primary Selective Laser Trabeculoplasty

For the predictors of initial IOP-lowering response, covariates that achieved $P < 0.10$ in the initial variable selection regression analyses were baseline IOP ($P < 0.001$), gender ($P = 0.002$), and age ($P = 0.05$) (Table 4). Within-group (OHT vs. OAG) subanalysis demonstrated that the trend noted toward increasing absolute IOP reduction with higher baseline IOP (Fig 1) was significant in both OHT (coefficient 0.68; 95% CI, 0.55–0.81; $P < 0.001$) and OAG (coefficient 0.58; 95% CI, 0.53–0.64; $P < 0.001$). The final multivariable linear regression model showed that baseline IOP ($P < 0.001$) and gender ($P = 0.04$) were predictors of initial absolute IOP reduction (Table 5).

Drop-Free Disease Control

Eyes that met target IOP without disease progression or need for topical IOP-lowering medication were deemed to have achieved drop-free disease-control. At 12 months, 85.2% of eyes (518 eyes) achieved drop-free disease-control after 1 or 2 SLTs. At 24 months and 36 months, 79.2% of eyes (456 eyes) and 74.6% of eyes (400 eyes), respectively, continued to achieve drop-free disease-control (Table 6). At all time points, drop-free disease-control was achieved in a higher percentage of OHT and mild OAG eyes compared with moderate and severe OAG eyes.

Drop-Free Disease Control after Initial Single Selective Laser Trabeculoplasty

Assessing drop-free disease-control achieved by *initial single SLT at baseline*, 75.5% of eyes (459 eyes) achieved this at 12 months, 66.5% of eyes (383 eyes) achieved this at 24 months, and 58.2% of eyes (312 eyes) achieved this at 36 months. At all time points, drop-free disease-control *after single initial SLT* was achieved in a higher percentage of OHT and mild OAG eyes compared with moderate and severe OAG eyes (Table 7).

Table 7. Eyes Achieving Drop-free Disease-Control after Single, Initial Selective Laser Trabeculoplasty at Baseline

Disease Severity	12 mos Total Eyes Available for Analysis (n)	12 mos Eyes Achieving Drop-free Disease Control after Single SLT % (n)	24 mos Total Eyes Available for Analysis (n)	24 mos Eyes Achieving Drop-free Disease Control after Single SLT % (n)	36 mos Total Eyes Available for Analysis (n)	36 mos Eyes Achieving Drop-free Disease Control after Single SLT % (n)
All eyes	608	75.5% (459)	576	66.5% (383)	536	58.2% (312)
OHT	192	85.9% (165)	174	80.5% (140)	158	72.8% (115)
Mild OAG	315	79.4% (250)	293	70.6% (207)	269	64.3% (173)
Moderate OAG	54	46.3% (25)	69	42% (29)	57	33.3% (19)
Severe OAG	47	40.4% (19)	40	17.5% (7)	52	9.6% (5)

OHT = ocular hypertension; OAG = open-angle glaucoma; SLT = selective laser trabeculoplasty.

Table 8. Mean Intraocular Pressure Reduction and Percentage Intraocular Pressure Reduction at 36 Months in Eyes Achieving Drop-free Disease-Control after Single Initial Selective Laser Trabeculoplasty

	Drop-free Disease Control Using Single SLT at 36 mos (Eyes)	Mean (SD) Absolute IOP Reduction (mmHg)	Mean (SD) % IOP Reduction from Baseline
All eyes	312	8.1 (4.1)	31.4 (11.7)
OHT	115	8.8 (3.6)	32.7 (11.5)
Mild OAG	173	7.5 (4.3)	29.9 (11.7)
Moderate OAG	19	8.6 (3.9)	36.4 (11.7)
Severe OAG	5	8.2 (4.6)	34.4 (13.1)

IOP = intraocular pressure; OAG = open-angle glaucoma; OHT = ocular hypertension; SD = standard deviation; SLT = selective laser trabeculoplasty.

Overall at 36 months, mean absolute IOP reduction in the 312 eyes achieving drop-free disease-control after single initial SLT at baseline was 8.1 mmHg (SD, 4.1). Mean absolute IOP reduction was similar between all disease severities (Table 8).

By 36 months, 23 eyes had objective evidence of disease progression (19 eyes visual field progression, 2 eyes had disc progression, 2 eyes had disc and VF progression), and 26 eyes had an upward revision of target IOP, if IOP control was not initially achieved in the absence of disease progression.[12] These results account for this, such that all eyes achieving drop-free disease-control met target IOP (achieving >20% IOP reduction from baseline IOP) without disease progression or need for topical medication. This is reflected in the number of eyes achieving drop-free disease-control at 36 months (74.6% eyes) and after single initial SLT (58.2% eyes) being slightly fewer compared with those solely achieving target IOP without topical medication at 36 months (78.2% eyes) and after single initial SLT (59.9%) as reported in the LiGHT main outcomes article.[13]

Predictors of Drop-Free Disease Control at 36 Months

A total of 312 eyes achieved drop-free disease-control at 36 months after initial single SLT (Table 8). These eyes achieved >20% IOP reduction from baseline IOP and thus were a treatment success (using conventional "IOP lowering >20% from baseline IOP" definition of success). Baseline covariates that achieved $P < 0.10$ in the mixed-effects univariable logistic regression analyses were total power of 1st SLT ($P = 0.08$) and age ($P = 0.09$) (Table 9). Two-month IOP ($P < 0.001$) was a posttreatment covariate that achieved $P < 0.10$ in the univariable logistic regression analysis. The final mixed-effects multivariable logistic regression model of baseline factors showed that total power of first SLT (Table 10) was a predictor of achieving drop-free disease-control at 36 months after single initial SLT (adjusted odds ratio, 1.02; 95% CI, 1.01−1.04; $P = 0.01$). Two-month IOP was also a posttreatment predictor of drop-free disease-control at 36 months when controlling for the other significant baseline factors (adjusted odds ratio, 0.66; 95% CI, 0.57−0.79; $P < 0.001$) (Table 10).

Selective Laser Trabeculoplasty Safety

There were no sight-threatening adverse events related to primary SLT during or after the procedure (Table 11). Six eyes (of 6 patients) experienced immediate post-laser IOP spike (>5 mmHg from pretreatment IOP) at 60 minutes, but only 1 of these eyes required medical treatment. No IOP spikes >10 mmHg from pretreatment IOP at 60 minutes postprocedure were reported. In 4 patients (1.1%), there was difficulty in visualizing the angle, and in 3 patients (0.9%), fewer laser applications than required by the protocol were reported to have been used. After SLT, symptoms including ocular discomfort, headache, blurred vision, and photophobia were reported by 34.4% of patients (122 patients). These were of a transient nature and self-limiting; all had resolved by the first scheduled visit. No IOP spikes (>5 mmHg from baseline IOP) were detected at the 2-week safety check visit post-SLT; 6.2% of eyes (38 eyes) were noted to have a higher IOP at 2-week safety visit compared with baseline.

Table 9. Univariable Selection Logistic Regression Analysis

Variable	Odds Ratio	95% CI	P Value
Baseline IOP (mmHg)	1.01	(0.95−1.09)	0.69
Race/ethnicity			0.74
Black	1.55	(0.57−4.20)	
Asian	0.74	(0.16−3.41)	
Other	1.78	(0.23−13.64)	
*Reference white European			
Sex			
Female	0.57	(0.26−1.28)	0.17
Age (yrs)	0.97	(0.94−1.00)	0.09*
CCT (μm)	1.00	(0.99−1.01)	0.62
PXF status			
Nil PXF	18.9	(0.28−1294.66)	0.17
Average TM Pigmentation grade			0.98
1- Mild	1.1	(0.47−2.57)	
2- Moderate	1.1	(0.34−3.26)	
3- Dense	1†		
*Reference no pigmentation			
Phakic status			
Phakic	0.52	(0.10−2.67)	0.44
Hypertension (Y/N)			
No	0.63	(0.28−1.43)	0.27
Diabetes mellitus (Y/N)			
No	1.07	(0.30−3.80)	0.91
Total power 1st SLT (mJ)	1.01	(1.00−1.03)	0.08*
Total No. of shots 1st SLT (shots)	1.02	(0.96−1.10)	0.41
2-mo IOP post-treatment (mmHg)	0.71	(0.61−0.82)	<0.001*

CCT = central corneal thickness; CI = confidence interval; IOP = intraocular pressure; PXF = pseudoexfoliation; SLT = selective laser trabeculoplasty; TM = trabecular meshwork.
*Covariates that achieved $P < 0.10$ in the initial variable selection logistic regression analyses were total power of 1st SLT ($P = 0.08$) and age ($P = 0.09$).
†Model unable to converge because of insufficient data.

Table 10. Multivariable Logistic Regression Analysis Result of Baseline Factors

Variable	Odds Ratio	95% CI	P value
Total power 1st SLT (mJ)	1.02	(1.01−1.04)	0.01
*2-mo IOP post-treatment (mmHg)	0.66	(0.57−0.79)	<0.001

CI = confidence interval; IOP = intraocular pressure; SLT = selective laser trabeculoplasty.
*Two-month IOP is a posttreatment predictor.

Discussion

This report analyzes the efficacy of primary SLT in one of the largest datasets of treatment-naive patients with OAG and OHT, with robust RCT-derived data. There was no significant difference in early absolute IOP lowering between OHT and OAG eyes having controlled for pretreatment baseline IOP and center effects (adjusted mean difference = −0.05 mmHg; 95% CI, −0.6 to 0.5 mmHg; $P = 0.85$). In addition, there was no significant difference in early absolute IOP lowering between topical medication and primary SLT (adjusted mean difference = −0.1 mmHg, CI, −0.6 to 0.4 mmHg, $P = 0.67$).

We found that higher baseline IOP was a predictor of early absolute IOP lowering at 2 months in a mixed-effects linear regression model. Increasing baseline IOP has been reported as being associated with increased IOP lowering[3] and was also demonstrated in this study, in which OHT eyes had greater IOP lowering from baseline compared with OAG eyes. This is also reflected in normal-tension glaucoma studies in which baseline IOPs are lower, and both absolute IOP reductions and success rates are lower compared with other subtypes.[24,25] Our study design minimized the effects of regression to the mean on IOP lowering: Qualifying IOP measurements were made on a separate day to baseline assessments, and IOP level was an entry criterion only for OHT eyes (31.9% of eyes at baseline). There was no placebo arm in LiGHT to ascertain fully the regression to the mean, but a previous study has demonstrated an approximately 1.4 mmHg (SD, 3.1) absolute IOP reduction at the first visit after placebo compared with 5 mmHg (SD, 3.6) in the topical latanoprost group.[26] We also found in our analysis that female gender was associated with lesser initial IOP lowering, not a commonly reported predictor of IOP lowering.[22]

Our results show that at 36 months follow-up, 74.6% of eyes (400 eyes) treated with primary SLT achieved drop-free disease-control, with 58.2% of eyes (312 eyes) doing so after a single initial SLT. All these eyes achieved IOP reduction >20% from baseline IOP. Intraocular pressure reduction >20% from baseline has been reported as occurring in between 38% and 74% of treated eyes at 36 months.[7,27-29] In our study, eyes with more advanced glaucoma had to meet more stringent target IOPs set according to previous published guidelines: moderate or severe disease had to achieve a minimum 30% reduction from baseline IOP to continue without further intervention.[12] Thus, more severely affected eyes achieving >20% but <30% IOP reduction after first SLT would have undergone a further treatment (second SLT or medication if nonresponse to first SLT). This is reflected in our results with only 58.2% of eyes not receiving additional therapy. The relative proportion of eyes achieving drop-free disease-control at 36 months after initial single SLT at baseline (Table 7) was greater in OHT and mild OAG eyes (with less stringent targets) than moderate and severe OAG eyes (with lower target IOPs), despite similar mean absolute IOP reductions for all levels of disease severity (Table 8). This does not mean SLT was ineffective in more advanced disease, merely insufficient in isolation.

The above was taken into account in the predictors of success mixed-effects logistic regression model, with terms for baseline disease severity and site (to control for center effects), while using the eye as the unit of analysis and using

Table 11. Summary of Laser-Related Adverse Events

Adverse Events during SLT	Total No. of Events (n=20)	Total No. of Patients Reporting (N=19) (5.4%)
Discomfort (ocular or headache)	6	6 (1.7%)
IOP spike (>5 mmHg)	6	6 (1.7%)
Other (specify):		
Fewer shots	3	3 (0.9%)
Visualization of angle	5	4 (1.1%)
Adverse Events Post-SLT	**Total No. of Events Total (n=172)**	**Total No. of Patients Reporting (N=122) (34.4%)**
Discomfort (ocular or headache)	92	82 (23.1%)
Blurred/altered vision	23	21 (5.9%)
Change in refraction	5	4 (1.1%)
Inflammation post-SLT	1	1 (0.3%)
Other (specify):	51	47 (13.2%)
Photophobia	21	20 (5.6%)
Hyperemia	3	3 (0.8%)

IOP = intraocular pressure; SLT = selective laser trabeculoplasty.

patients as a random factor to adjust for correlation between paired eyes. Our logistic regression model suggested a statistically significant but small increase in odds of achieving drop-free disease-control at 36 months with higher total power of first SLT (adjusted odds ratio, 1.02; 95% CI, 1.01−1.04, $P = 0.01$). On further analysis, mean total power of 1st SLT in success eyes was 92.6 mJ (SD, 21.8) versus 87.7 mJ (SD, 25.6) in non-success eyes (adjusted mean difference = 2.37 mJ, 95% CI, −0.5 to 5.2 mJ). The modest effect and overlap in treatment parameters between success and non-success eyes means that response prediction is not possible (Appendices 4 and 5, available at www.aaojournal.org). The trend to a greater response with more power delivered would need confirmation in future studies. There is mixed evidence regarding the optimum power settings for SLT treatment. Tang et al[30] compared 39 patients receiving 100 shots of 360° SLT using low energy settings (0.3−0.5 mJ) with 35 patients who received 100 shots of 360° SLT using standard energy settings (0.6−1.0 mJ). No difference in IOP lowering between groups at all time points up to 1 year was noted. Furthermore, there was reduced incidence of adverse events in the lower energy group. Realini et al[31] found total laser power not to be a significant predictor of 12-month success, with a mean (SD) of 86.0 (21.1) mJ in the right eye and 87.7 (20.6) mJ in the left eye compared with a mean (SD) of 90.4 (23.5) mJ in our study.[8] In contrast, Lee et al[32] found that greater total SLT energy was associated with a greater IOP lowering but this study was limited by small sample size, short follow-up (1 month), and total energy powers that were considerably higher than used here (optimum total reported as 226.1 mJ). Habib et al[33] divided patients receiving 360 degree SLT treatment into those who received low (<85 mJ), medium (85−105 mJ), or high (>105 mJ) energy SLT. At all time points up to 36-month follow-up, there was a significant positive correlation between greater energy and IOP lowering.[33]

We wanted to establish whether IOP at first scheduled visit after SLT at 2 months was predictive of achieving disease-control at 36 months after initial single SLT at baseline. A previous study found that the only significant predictor of IOP lowering at 12 months across all eyes was time, with the maximum IOP reduction seen at 3 months followed by a slow decline in effect subsequently.[31] Although we found successful eyes achieving drop-free disease-control after initial single SLT at 36 months had a lower IOP at 2 months compared with non-successful eyes (adjusted mean difference = −1.9 mmHg; 95% CI, −1.4 to −2.3 mmHg), there may not be enough specificity in this observation (because of the SD of IOP measurements) to be helpful in the individual case.

Selective laser trabeculoplasty was well tolerated in this study, with no sight-threatening adverse events and only 6 eyes (1% of total eyes receiving SLT) having an IOP spike (>5 mmHg) immediately after SLT. This compares favorably with other studies, which have reported IOP spikes (>5 mmHg) occurring in up to 28% of eyes.[3] After SLT, 34.4% of patients described mild laser-related adverse events, including ocular discomfort, headache, blurred vision, and photophobia. These were of a transient nature and self-limiting. Anterior chamber inflammation is common after SLT, with up to 83% of eyes demonstrating some degree of inflammation.[34] Considering the biological changes that SLT induces,[35] some regard transient self-limiting inflammation to be a predictable consequence of SLT, explaining the symptoms of ocular redness, photophobia, and pain that patients may report. During the LiGHT trial overall, there were fewer drop-related ophthalmic and systemic adverse events reported by patients in the initial SLT arm versus the initial medication arm.[13]

Direct comparison between SLT studies is difficult. Differences in study design exist between studies, including patient demographics, disease subtypes investigated (OHT vs. OAG), variations in topical IOP lowering medication use before SLT (treatment-naive vs. medication washout period before SLT vs. adjunct SLT in uncontrolled eyes on maximum tolerated medical therapy), differences in SLT treatment parameters (180-degree vs. 360-degree treatments, variability in numbers of shots fired), variability in follow-up intervals, total duration of follow-up, and variable definitions of success.

This report has several strengths. It uses data derived from a prospective multicenter RCT with broad entry criteria that maximize its generalizability. Eyes were treated to predefined target IOPs based on disease severity with predefined treatment escalation criteria and SLT treatment parameters.[12] An obvious limitation is that this analysis was post hoc, and the sample size of LiGHT was determined on the basis of a power calculation to analyze the primary outcome of HRQL. We did not perform a post hoc power calculation for the IOP-lowering parameters considered in this report, because limitations have been reported with such calculations.[36] Instead, the narrow (<1 mmHg) CIs for our pointwise estimates of differences in early IOP lowering between OHT versus OAG eyes and primary SLT versus topical medication suggest that the study had an adequate sample size to detect a clinically important difference if it exists.[37] For our logistic regression analysis, we had sufficient events based on the rule of thumb that 10 to 15 events per variable are required to develop an adequate prediction model.[38] In this analysis, despite no clinically or statistically significant differences in gender or ethnicity being noted in eyes available versus unavailable to analyze at 36 months, relatively more female and black patients had eyes unavailable for analysis. Studies have shown disparities in the use of eye care services among different racial minorities, with socioeconomic deprivation and differences in access to healthcare implicated as contributory to this.[39,40]

In conclusion, we report that primary SLT is an effective initial therapy for treatment-naive patients with OAG and OHT. Primary SLT provides a comparable initial IOP-lowering response in OHT versus OAG eyes and to topical medication. It achieves drop-free disease-control in approximately 75% of eyes at 36 months, with the majority of eyes (58.2%) doing so after a single initial SLT. Selective laser trabeculoplasty had a good safety profile during our study, while avoiding the potential adherence issues associated with topical medication. Despite the exploratory

nature of these analyses, our results are clinically valuable and add to the limited body of evidence on primary SLT in treatment-naive OAG and OHT, supporting its use as an effective and safe initial treatment for such conditions.

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Abbreviations and Acronyms:
CI = confidence interval; **dB** = decibels; **HRQL** = health-related quality of life; **IOP** = intraocular pressure; **LiGHT** = Laser in Glaucoma and Ocular Hypertension; **OAG** = open-angle glaucoma; **OHT** = ocular hypertension; **RCT** = randomized controlled trial; **SD** = standard deviation; **SLT** = selective laser trabeculoplasty; **TM** = trabecular meshwork; **VF MD** = visual field loss with mean deviation.

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