Residual lesions after pharmacological and dye-laser treatment of Infantile Hemangiomas: critical review of 432 cases

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Running head: residual lesions after treatment of infantile hemangiomas

Abstract

Objectives. Infantile hemangiomas (IHs) are the most common benign tumors in infanthood. Although they are often self-limiting, management of IHs is still controversial because residual lesions may persist in some cases. The aim of this study is to report our experience with patients affected with IH and investigate the frequency of residual lesions in treated versus untreated patients.

Methods. This retrospective observational study enrolled patients with IHs evaluated over the past 10 years. Patients were managed with systemic or local pharmacotherapy, laser therapy, a combination of them, or with observation only.

Results. A total of 432 patients were included: 71% received one or more therapies for IHs. 75.2% of untreated patients had at least one residual lesion, compared to 41.4% of treated patients ($p < 0.001$). Patients treated with laser therapy or topical timolol had the lowest rate of residual lesions.

Conclusions. This rather large case series suggests that IHs management with pharmacotherapy and especially laser therapy is associated with lower number of residual lesions than observation only. Although propranolol can be very useful to avoid life-threatening complications and severe tissue impairment, laser therapy and topical timolol are potential effective treatments to decrease the incidence of residual lesions, mostly associated with superficial IHs.

Introduction

Infantile hemangiomas (IHs), benign proliferations of endothelial tissue, have a growth pattern typically characterized by an early proliferative phase, driven by angiogenic growth factors (1) (2) (3) during the neonatal period or early infancy, followed by spontaneous partial or complete involution immediately after the proliferation phase, or after a plateau period (4) (5) (6). IHs occur in approximately 1–3% of newborns, with a prevalence of 10–12% by one year of age, and a predominance among preterm births, females, twins and Caucasians (4) (7).

IHs are usually classified as either superficial, deep, or mixed, and further subclassified into localized or segmental forms (8) (9). Although the lesions are often self-limiting, residual lesions such as telangiectasia, residual fibrous or fatty tissue, atrophy, discoloration, distortion of the anatomical profile or alopecia occur in some cases (10) (11) (12). In a follow-up study of residual lesions up to 74% has been reported. These residual lesions are permanent and do not involute spontaneously representing an aesthetic and socializing problem, and surgical treatment is often required (13).

Furthermore, lesions that threaten to compromise vision or airway patency, or which cause ulcerations or permanent disfigurement, may also occur. Management of IHs has evolved in last decades.

Treatment with high-dose of systemic corticosteroids has been widely used, despite the associated risk of side effects (14) (15) (16). Since 2007, propranolol was identified as an alternative effective agent for treating IH (17) and has largely replaced or in a few cases used in combination with corticosteroid therapy (18) (19).

Since the identification of propranolol as a treatment for IHs by Léauté-Labréze et al. (17), numerous authors have confirmed their findings (20) (21) (22). Its mechanisms include vasoconstriction, inhibition of angiogenesis and apoptosis.

Lately topical timolol, an off-label therapy used to this day to treat glaucoma, was found effective in superficial IHs management with a similar pathogenetic mechanism (23) (24), with a

high profile of tolerability and safety (25).

Finally, laser therapy with dye-lasers having wavelengths overlapping the absorption spectrum of oxyhemoglobin has been proposed for treating IHs. This technique is considered the first choice of laser for treating capillary vascular malformations and residual telangiectasias of IHs, using a selective photothermolysis mechanism (26) (27) (28) (29) (30) (31). It is also effective for fatty-fibrous deposits and on correction of anatomical distortion, due to the thermo-induced lysis of collagen which promotes the remodeling of the tissue, linked to the reduction of TGF-B1 (growth factor-B1) and CTGF (connective tissue growth factor) (32) (33). Laser therapy is also the standard of care for ulcerated lesions (34); in addition, combining dye-laser therapy with propranolol can improve outcomes (20) (35). Although these therapeutic approaches seem useful in the management of IHs, data on their real efficacy are limited. Aim of this study was to describe our experience with patients affected with IHs and investigate the frequency of residual lesions in treated versus patients managed with only observation.

Materials and Methods

In this retrospective observational study, we enrolled patients with IHs who were evaluated over the past 10 years (from January 2007 to December 2017) in the pediatric dermatology Unit of the Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Patients

All eligible subjects were patients diagnosed with IHs in their first 60 days of life and with a follow-up evaluation of at least five years.

Patients managed with i) only observation, ii) pharmacological treatment, iii) dye-laser or iv) a combination of the two latter, were included. Patients affected by syndromic IHs, non-involuting congenital hemangiomas, rapid-involuting congenital hemangiomas, partially involuting congenital hemangiomas or patients that had received other types of therapy like surgery were excluded from the study. From each eligible case, we extracted data on demographics, type and site of the IH, management, follow-up and outcomes.

Management

Only observation. Patients who did not receive any drug or treatment potentially influencing the course or extension of IHs were considered as managed with only observation.

Pharmacotherapy. Patients managed with pharmacological treatment received steroids, propranolol, or topical timolol. The treatments were initiated between ages 15 to 90 days. Patients receiving corticosteroid therapy were administered oral betamethasone 0.1-0.2 mg/kg/day. Patients treated with propranolol, underwent routine blood testing, thyroid function tests, and examination by a pediatric cardiologist before the beginning of the treatment. The cardiologist evaluated medical history and performed a physical examination along with heart rate, blood pressure, electrocardiogram, and echocardiogram. Patients without contraindications were prescribed oral propranolol 2 mg/kg/day. Heart rate and blood pressure were monitored monthly. Patients under topical timolol (Timogel®, 1

mg/g) were treated with 2 drops timolol twice a day on the lesion directly.

Dye-laser. A dermatologist (RC) performed all laser procedures in the multiuse outpatient facility in the pediatric clinic. An anesthetic cream (2.5% lidocaine, 2.5% prilocaine, Emla®, AstraZeneca S.p.A., Milan) was applied one hour before laser therapy and topical gentamicin was applied afterwards. A flash-pumped dye laser was adopted performing a double passage treatment in the same session, 7.5 - 8.5 J/cm2 10 msec followed by 7.5 – 8.5 J/cm2 1.5 msec. Laser therapy was used in all deep, periorificial, and segmental IHs, in addition to those with small or intermediate size that had relevant esthetic impact. Dye laser sessions were performed twice a year and up to a total maximum of six session on the basis of the clinical evolution of the lesions. Due to the large number of patients demanding laser treatments in our clinic we were forced to reduce the number of sessions for each patient. In order to exploit the properties of systemic therapy (if provided for) we preferred to use laser treatment during the involution phase. We were also forced to perform laser only twice yearly for the same reason. Laser treatments ware stopped when there was no residua at the clinical revaluation.

Follow-up and outcomes

Patients who underwent only observation were monitored in the outpatient dermatology clinic every 3-6 months in the first 2 years, then every 6–12 months. Patients receiving propranolol were monitored after one month, three months, and at the end of therapy. The duration of therapy was based on patient age, response to therapy, and lesion location. Patients managed with dye laser were monitored every 4-6 months. At each follow-up appointment the lesions volume, color, and consistency, were assessed and rated by at least two pediatric dermatologists. Patients with complete lesion regression were follow-up annually.

For the purpose of this study, healing was considered as the absence of clinically detectable lesions, absence of tumefaction, intact skin, and absence of residual lesions. The presence for at least five years of the following skin alterations were considered as residual lesions: telangiectasia, fibro-fatty

residues, atrophic scarring or discoloration of the skin (11) (36) (37). They compared in person the lesion versus initial photograph.

The pediatric dermatologists who performed the follow-up evaluations were aware of previous or ongoing treatments.

Statistical Analysis

Categorical variables were presented as absolute numbers or percentages and were analyzed using the contingency table analysis with the Chi-square or Fisher's test, as appropriate.

All tests were two-sided and a p-value of less than 0.05 was considered as statistically significant. Data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) statistical software.

Results

The study population consisted of 432 (315 female) patients. Approximately half (52%) of the lesions were located on the face or scalp. Multiple lesions were detected in 9.5% of cases. Of the 432 patients enrolled, 307 (71.1%) received at least a therapy for IHs (table 1). Treatment was more common in the group of patients with deep, segmental, large, or periorificial lesions (97.5%), than in ones mixed (62.3%) or superficial (46.6%) lesions. The algorithm showing the treatment approach is given in suppl. Fig. 1.

A total of 125 (28.9%) patients were managed with observation only. Pharmacology treatment was given in 129 (29.9%) patients and dye laser in 178 (41.2%) patients.

More than one therapy was administered in 115 (16.6%) patients: laser and other therapies (except for propranolol) in 20 (17.3%), laser and other therapies (including propranolol) in 52 (45.3%) patients, and laser therapy and propranolol in 43/115 (37.4%) patients. Propranolol was administered for 6 months in 107/162 patients (66%), between 7 and 9 months in 29/162 patients (17.9%), and 10-13 months in 24/162 patients (16%). The duration of corticosteroid therapy ranged from 20–40 days. A single laser therapy session was performed on 85 out of 178 patients (47%), two sessions were performed in 59 out of 178 patients (33%), and 34 of 178 (20%) received three or more procedures. Seventy-one out of 307 (23.1%) patients were treated with topical timolol for a period between 1 and 15 months with a mean of 6.59 months.

Residual lesions

Overall, 75.2% of untreated patients remained with at least one of the characteristics described (ie. Telangiectasia, Fibro-fatty tissue) as residual lesion, compared to 41.4% of treated patients ($p < 0.001$) at 5 years follow up. Patients treated with only laser therapy had the lowest rate of residual lesions as compared to untreated patients (25.8% vs 75.2%, respectively, $p < 0.001$). We also observed a lower rate of residual lesions in patients under topical timolol as compared to untreated patients (27.8% vs 75.2%, respectively, $p < 0.001$) as shown in Table 2. A combined

therapy with propranolol and dye-laser was associated with a lower percentage (46.5%) of residual lesions than the therapy with propranolol alone (56.7%), as shown in Fig. 2.

Discussion

This study involving more than 400 patients affected with IHs points out that patients managed with only observation present a higher number of residual lesions than ones receiving pharmacological treatments or dye laser. At the same time, management with laser therapy or topical timolol is associated with the lowest number residual lesions; moreover, most patients with residual disease had superficial lesions, which in current practice are less likely to receive treatment.

According to previous studies (31) (38), dye-laser therapy and topical timolol are effective on superficial lesions (39) (40), and dye-laser is effective during the involution phase of the lesions. Previous observations pointed out that laser-therapy might also reduce the proliferative phase of childhood hemangiomas (41). In this study, laser therapy was limited to the involution phase of hemangiomas and therefore we cannot support nor infer the effectiveness of laser therapy in the early management of hemangiomas. On the other hand, propranolol is currently the gold standard treatment in the growth phase of deep, segmental, periorificial, or life-threatening IHs, both for its effectiveness and for its higher safety compared to corticosteroids (42). However, these types of IHs tend to heal completely, whilst the most superficial, mixed, or cobblestone-like forms tend to be associated with residual lesions, which can have a significant impact on patients and their families due to their large size and negative esthetic consequences (10) (36) (43). Finally, also in IHs undergoing systemic treatment, laser therapy has been claimed as a potential therapy to improve the aesthetic outcome, in combination with systemic beta-blocker therapy (37) (44). Thus, treatment of lesions or residual lesions with a dye-laser can prevent outcomes that are less esthetically appealing, and, if on the face or exposed limbs, may cause psychological distress in young patients.

Pharmacological treatment blocks the expansion of lesions and reduces the time required for healing. It is generally reserved for cases in which IHs cause a health risk or tissue damage. In this study, the tendency to use propranolol in patients with complex IH could partly underly its apparent lower clearance rates of residua if compared with the use of only laser therapy. A combination of

these therapies, especially in patients with more complex IHs, could represent the most effective therapeutic mode in order to both reduce the healing time and prevent the permanent lesions. Indeed, while treating large deep lesions during the growth phase with pharmacological therapy is effective for preventing complications due to their rapid growth, treating superficial lesions in the post-expansive phase with dye-lasers can greatly reduce the occurrence of permanent lesions in complex IHs.

Lastly, we observed that topical timolol was also able to reduce residual. The results obtained are referred mostly to simple and superficial IHs often not treated to date. These untreated patients represent the most suitable class to make a comparison with the patients under topical timolol because their lesions are mostly small and superficial too. Topical therapy can be considered in association to other pharmacological or laser therapies. However, it can also represent an efficient treatment for lesions that current practice recommends for a “wait and see” approach, and actually are those that might lead to permanent lesions.

The strength of this study is that it includes a rather large sample of patients affected by IHs and managed by different treatment strategies. Yet, the study has at least several limitations. First, it is a retrospective monocentric study not blinded to treatment modality. Second, small superficial lesions were somewhat underrepresented in our population, likely because these are often managed by the primary pediatrician. Third, laser treatments have been performed during the involution phase only and IHs chosen for observation only represent the simpler and most superficial hemangiomas.

In conclusion, dye-laser and topical timolol are promising treatments to reduce the risk of residual lesions in patients affected with IHs. Their application might also be beneficial in patients previously managed with propranolol and with persisting lesions. Randomized controlled studies are needed to further support their use in day to day care of children with IHs.

References

1. *Local serum levels of vascular endothelial growth factor in infantile hemangioma: intriguing mechanism of endothelial growth.* **Przewratil P, Sitkiewicz A, Andrzejewska E.** 2010, Cytokine, Vol. 49, pp. 141-7.
2. *Endothelial progenitor cells in infantile hemangioma.* **Yu Y, Flint AF, Mulliken JB, et al.** 103, 2004, Blood, pp. 1373-5.
3. *Increased Tie2 expression, enhanced response to angiopoietin-1, and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells.* **Yu Y, Varughese J, Brown LF, et al.** 2001, Am J Pathol, Vol. 159, pp. 2271-80.
4. *Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas.* **Frieden IJ, Haggstrom AN, Drolet BA, et al.** 2005, Pediatr Dermatol, Vol. 22, pp. 383-406.
5. *Cutaneous hemangiomas in premature and mature infants.* **K., Holmdahl.** 1955, Acta Paediatr, Vol. 44, pp. 370-9.
6. *Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics.* **Mulliken JB, Glowacki J.** 1982, Plast Reconstr Surg , Vol. 69, pp. 412-22.
7. *A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature.* **Kanada KN, Merin MR, Munden A, et al.** 2012, J Pediatr, Vol. 161, pp. 240-5.
8. *Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex.* **Chiller KG, Passaro D, Frieden IJ.** 2002, Arch Dermatol, Vol. 138, pp. 1567-76.
9. *Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development.* **Haggstrom AN, Lammer EJ, Schneider RA, et al.** 2006, Pediatrics, Vol. 117, pp. 698-703.
10. *Untreated hemangiomas: growth pattern and residual lesions.* **Bauland CG, Luning TH, Smit JM, et al.** 2011, Plast Reconstr Surg, Vol. 127, pp. 1643-8.
11. *The natural history of the strawberry naevus.* **Bowers RE, Graham EA, Tomlinson KM.** 1960, Arch Dermatol, Vol. 82.
12. *Guidelines of care for cutaneous haemangiomas.* **Chan YC, Giam YC.** 2005, Ann Acad Med Singapore, Vol. 34, pp. 117-23.
13. *Risk Factors for Degree and Type of sequelae after involution of untreated hemangiomas of infancy.* **Baselga E., MD e E. Roe, MD, et al.** 2016, JAMA Dermatol, Vol. 152, pp. 1239-1243.
14. *Guidelines of care for hemangiomas of infancy.* **Frieden IJ, Eichenfield LF, Esterly NB, et al.** 1997, J Am Acad Dermatol, Vol. 37, pp. 631-7.

15. *Role of steroid in childhood haemangioma: a 10 years review.* **Gangopadhyay AN, Sinha CK, Gopal SC, et al.** 1997, Int Surg, Vol. 82, pp. 49-51.
16. *Induced resolution of cavernous hemangiomas following prednisolone therapy.* **Zarem HA, Edgerton MT.** 1967, Plast Reconstr Surg , Vol. 39, pp. 76-83.
17. *Propranolol for severe hemangiomas of infancy.* **Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al.** 2008, N Engl J Med, Vol. 358, pp. 2649-51.
18. *Propranolol therapy for cutaneous infantile haemangiomas initiated safely as a day-case procedure.* **McSwiney E, Murray D, Murphy M.** 2014, Eur J Pediatr, Vol. 173, pp. 63-8.
19. *Propranolol for infantile hemangioma (PINCH): an open-label trial to assess the efficacy of propranolol for treating infantile hemangiomas and for determining the decline in heart rate to predict response to propranolol.* **Sondhi V, Patnaik SK.** 2013, J Pediatr Hematol Oncol, Vol. 35, pp. 493-9.
20. *Propranolol for severe infantile hemangiomas: follow-up report.* **Sans V, de la Roque ED, Berge J, et al.** 2009, Pediatrics, Vol. 124, pp. 423-31.
21. *Infantile hemangioma: pathogenesis and mechanisms of action of propranolol.* **Rotter A1, de Oliveira ZNP1.** 2017, J Dtsch Dermatol Ges, Vol. 15(12), pp. 1185-1190.
22. *A randomised controlled trial of propranolol for infantile hemangioma.* **M, Hogeling.** 2011, Pediatrics, Vol. 128, p. 259.
23. *Topical Timolol for Infantile Hemangiomas: Evidence for Efficacy and Degree of Systemic Absorption.* **Weibel L, Barysch M, Scheer H, et al.** 2016, Pediatric Dermatology, Vol. 33(2), pp. 184-190.
24. *Adverse Events in Young and Preterm Infants Receiving Topical Timolol for Infantile Hemangioma.* **Peter Frommelt, Anna Juern, Dawn Siegel.** 2016, Pediatric Dermatology, Vol. 33(4), pp. 405-414.
25. *Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eye drops.* **Korte JM, Kaila T, Saari KM.** 2002, Graefes Arch Clin Exp Ophthalmol, Vol. 240, pp. 430-435.
26. *I laser in dermatologia, linee guida di dermatologia ambulatoriale.* **Mairini L, Bellini M, Cannarozzo G, et al.** 1998, Dermatologia Ambulatoriale, Vol. 98.
27. *Clinical, histologic, and ultrastructural changes after nonablative treatment with a 595-nm flashlamp-pumped pulsed dye laser: comparison of varying settings.* **Goldberg DJ1, Sarradet D, Hussain M, Krishtul A, Phelps R.** 2004, Dermatol surg , Vol. 30(7), pp. 979-82.
28. *Treatment of scars: a review.* **Alster TS, West TB.** 1997, Ann Plast Surg, Vol. 39(4), pp. 418-32.
29. *Laser treatment of hypertrophic scars, keloids and striae.* **Alster TS, Handrick C.** 2000, Semin Cutan Med Surg, Vol. 19(4), pp. 287-92.
30. *Treatment of cutaneous hemangiomas by the flashlamp-pumped pulsed dye laser: prospective analysis.* **Garden JM, Bakus AD, Paller AS.** 1992, J Pediatr, Vol. 120, pp. 555-60.
31. *Five years' experience of treating port wine stains with the flashlamp-pumped pulsed dye laser.* **Katugampola GA, Lanigan SW.** 1997, Br J Dermatol, Vol. 137, pp. 750-4.
32. *Flashlamp Pulsed Dye Laser (PDL) suppression of Keloid roliferation through down-regulation of TGF-B1 expression and extracellular matrix expression.* **Yur-Ren Kuo, Seng Feng J et al.** 2004, Lasers in Surgery and Medicine, Vol. 34, pp. 104-108.
33. *The effect of Flashlamp Pulsed Dye laser on the expression of connective tissue growth factor in keloids.* **Qiarong Yang, Ying Ma et al.** 2012, Lasers in Surgery and Medicine, Vol. 44, pp. 377-383.
34. *Use of flashlamp-pumped pulsed dye laser in the treatment of superficial vascular malformations and ulcerated hemangiomas.* **Di Maio L, Baldi A, Dimaio V, et al.** 2011, In Vivo, Vol. 25, pp. 117-23.
35. *Therapy of ulcerated hemangiomas.* **McCuaig CC, Cohen L, Powell J, et al.** 2013, J Cutan Med Surg, Vol. 17, pp. 233-42.
36. *Laser treatment of infantile hemangioma: A systematic review.* **Chinnadurai S, Sathe NA, Surawicz T.** 2016, Lasers Surg Med, Vol. 48, pp. 221-33.
37. *Propranolol therapy for infantile hemangioma: our experience.* **Zhang L, Wu HW, Yuan W,**

Zheng JW. 2017, Drug Des Devel Ther, Vol. 8(11), pp. 1401-1408.
38. *Clinical efficacy of the pulsed dye laser in the treatment of vascular lesions.* **Garden JM, Bakus AD.** 1993, J Dermatol Surg Oncol, Vol. 19, pp. 321-6.
39. *Infantile hemangiomas-role of propranolol.* **Menon P, Rao KL.** 2013, Indian Pediatr, Vol. 50(5), p. 521.
40. *Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study.* **Chakkittakandiyil A, Phillips R, Frieden IJ, et al.** 2012, Pediatr Dermatol, Vol. 29(1), pp. 28-31.
41. *Outcomes of childhood hemangiomas treated with the pulsed-dye laser with dynamic cooling: a retrospective chart analysis.* **al., Rizzo et.** 12, 2009, Vol. 35, pp. 1947-54.
42. *Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events - a review of the literature.* **Raphael MF, Breur JM, Vlasveld FA, et al.** 2016, Expert Opin Drug Saf, Vol. 15, pp. 199-214.
43. *Retrospective study of the treatment of infantile hemangiomas using a combination of propranolol and pulsed dye laser.* **al., Reddy et.** 6, 2013, Dermatol Surg., Vol. 39, pp. 923-933.
44. *Effective treatment for infantile hemangioma with long-pulsed dye laser with oral propranolol medication: a preliminary report.* **Furuta S, Sato H, Tsuji S, Murakami F, Kitagawa H.** 2016, Pediatr Surg Int, Vol. 32(9), pp. 857-62.

Figure legends

Figure 1. Algorithm showing the treatment approach

Figure 2. The percentage of residual lesions in treated vs. untreated patients, according to treatment modality.

Table legend

Table 1. Characteristics of the patients with infantile hemangiomas (N=432), management and residual lesions at follow-up

Table 2. Outcome, efficacy and safety

Table 1. Characteristics of the patients with infantile hemangiomas (N=432), management and residual lesions at follow-up

	No therapy	Timolol	Laser + other therapy (not propranolol)	Propranolol + other therapy	Only propranolol	Propranolol + laser	Only laser
Patients, N (%)	125 (29)	36 (8)	20 (5)	52 (12)	67 (15)	43 (10)	89 (21)
Males, N (%)	35 (28.0)	10 (27.8)	9 (45.0)	8 (15.4)	20 (29.9)	11 (25.6)	24 (27.0)
Type of Hemangioma							
Superficial, N (%)	55 (44.0)	27 (75.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (21.3)
Mixed, N (%)	66 (52.8)	9 (25.0)	16 (80.0)	9 (17.3)	17 (25.4)	10 (23.3)	48 (53.9)
Deep, segmental or periorificial, N (%)	4 (3.2)	0 (0.0)	2 (10.0)	43 (82.7)	50 (74.6)	33 (76.7)	22 (24.7)
Localization							
Face / scalp, N (%)	48 (38.4)	12 (33.3)	9 (45.0)	35 (67.3)	52 (77.6)	25 (58.1)	42 (47.2)
Trunk / arms, N (%)	64 (51.2)	18 (50.0)	9 (45.0)	4 (7.7)	7 (10.4)	10 (23.3)	35 (39.3)
Other / multiple localizations, N (%)	13 (10.4)	6 (16.7)	2 (10.0)	13 (25.0)	8 (11.9)	8 (18.6)	12 (13.5)
Residual lesions							
None, N (%)	31 (24.8)	26 (72.2)	11 (55.0)	25 (48.1)	29 (43.3)	23 (53.5)	66 (74.2)
≥ 1, N (%)	94 (75.2)	10 (27.8)	9 (45.0)	27 (51.9)	38 (56.7)	20 (46.5)	23 (25.8)

Table 2. Outcome, efficacy and safety.

	No therapy N=125	Timolol N=36	Laser + other therapy (not propranolol) N=20	Propranolol + other therapy N=52	Only propranolol N=67	Propranolol + laser N=43	Only laser N=89	All therapies N=307
Median healing time (months) (IQR)	39 (28-50)	15 (12-18.5)*,1	28.5 (18.5-36)*,1	30.5 (18-36)*,1	19 (14-24)*,1	22 (16-34)*,1	30 (23-38)*,1	*23 (16-34)*,1
Complications								
None, N (%)	120 (96.0)	35 (97.2)	19 (95.0)	41 (78.8)	58 (86.6)	31 (72.1)	71 (79.8)	*<0.001*
≥1, N (%)	5 (4.0)	1 (2.8)	1 (5.0)	11 (21.2)	9 (13.4)	12 (27.9)	18 (20.2)	
p-value[2]		*1.000*	*1.000*	*0.001*	*0.022*	*<0.001*	*<0.001*	
Ulceration, N (%)	4 (3.2)	1 (2.8)	1 (5.0)	10 (19.2)*	9 (13.4)*	11 (25.6)*	17 (19.1)*	*<0.001*
Bleed, N (%)	2 (1.6)	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	1 (2.3)	1 (1.1)	*1.000*
Astigmatism/Amblyopia,N(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	*1.000*
Residual lesions								
None, N (%)	31 (24.8)	26 (72.2)	11 (55.0)	25 (48.1)	29 (43.3)	23 (53.5)	66 (74.2)	*<0.001*
≥1, N (%)	94 (75.2)	10 (27.8)	9 (45.0)	27 (51.9)	38 (56.7)	20 (46.5)	23 (25.8)	
p-value[2]		*<0.001*	*0.006*	*0.002*	*0.008*	*0.001*	*<0.001*	
Teleangectasia, N (%)	87 (69.6)	7 (19.4)*	5 (25.0)*	15 (28.8)*	31 (46.3)*	7 (16.3)*	7 (7.9)*	*<0.001*
Fibro-fatty residues, N (%)	17 (13.6)	3 (8.3)	5 (25.0)	9 (17.3)	9 (13.4)	8 (18.6)	11 (12.4)	*0.776*
Atrophic scarring, N (%)	5 (4.0)	0 (0.0)	1 (5.0)	2 (3.8)	3 (4.5)	6 (14.0)*	7 (7.9)	*0.368*
Discoloration, N (%)	3 (2.4)	1 (2.8)	0 (0.0)	3 (5.8)	4 (6.0)	2 (4.7)	2 (2.2)	*0.570*
Dysmetria, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.8)*	2 (3.0)	4 (9.3)*	1 (1.1)	*0.070*

* p-value <0.05.
1 Wilcoxon nonparametric test
2 Chi-square test or Fisher's exact test