A systematic review of the safety and efficacy of currently used treatment modalities in the treatment of patients with PIK3CA-related overgrowth spectrum

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ABSTRACT

Background: PIK3CA (activating mutations of the p110α subunit of phosphatidylinositol 3-kinases)-related overgrowth spectrums (PROS) include a variety of clinical presentations that are associated with hypertrophy of different parts of the body. We performed a systematic literature review to assess the current treatment options and their efficacy and safety for PROS.

Methods: A literature search was performed in Embase, MEDLINE (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Google Scholar to retrieve studies on the treatment of hypertrophy in PROS. Randomized controlled trials, cohort studies, and case series with ≥10 patients were included in the present review. The titles, abstracts, and full text were assessed by two reviewers independently. The risk of bias was assessed using the Newcastle-Ottawa scale.

Results: We included 16 studies of the treatment of hypertrophy in PROS patients, 13 (81.3%) from clinical retrospective studies and 3 (13.7%) from prospective cohort studies. The risk of bias grade was low for 2, medium for 12, and high for 2 studies. Of the 16 studies, 13 reported on surgical treatment and 3 reported pharmacologic treatment using phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway inhibitors in PROS patients. In 3 studies, PROS was defined by a mutation in the *PIK3CA* gene, and 13 studies relied on a clinical definition of PROS. Surgical therapy was beneficial for a specific subgroup of PROS (macrodactyly). However, little has been reported concerning surgery and the potential benefits for other PROS entities. The reported side effects after surgical therapy were mostly prolonged wound healing or scarring. PI3K/mTOR pathway inhibition was beneficial in patients with PROS by reducing hypertrophy and systemic symptoms. The adverse effects reported included infection, changes in blood count, liver enzymes, and metabolic measures.

Conclusions: Surgery is a locally limited treatment option for specific types of PROS. A promising treatment option for PROS is pharmacologic PIK3CA inhibition. However, the level of evidence on the treatment of overgrowth in PROS patients is limited. (J Vasc Surg Venous Lymphat Disord 2022;10:527-38.)

Keywords: Phosphatidylinositol 3-kinase; Phosphoinositide-3 kinase inhibitors; TOR serine-threonine kinases

Somatic activating mutations of the phosphatidylinositol-3-kinase (PI3K)/AKT (protein kinase B)/mTOR pathway lead to angiogenesis and tissue overgrowth. PIK3CA (activating mutations of the p110α subunit of phosphatidylinositol 3-kinases)-related overgrowth spectrum (PROS) is a term used to describe a variety of clinical entities caused

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by postzygotic mosaic mutations of the *PIK3CA* gene that have hypertrophy of different parts of the body in common.[1] In general, PROS includes a heterogeneous group of clinical overgrowth phenotypes and syndromes such as congenital lipomatous overgrowth, vascular malformations, epidermal nevi and spinal abnormalities (CLOVES) syndrome,[1] Klippel-Trenaunay syndrome (KTS),[2] fibroadipose overgrowth,[3] hemimegalencephaly,[4] macrodactyly,[5] megalencephaly-capillary malformation,[6] hemihyperplasia multiple lipomatosis, facial infiltrating lipomatosis,[7] and capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of the face and limbs, and partial or generalized overgrowth[8] (Fig 1).

PROS is an umbrella term for a heterogeneous mix of syndromic diseases. Each presents with different clinical symptoms and signs that can be more or less disabling to the patient. Therefore, symptomatic and patient-centered management and treatment approaches are needed. The current established treatment modalities include surgical (ie, corrective surgery, lesion debulking, amputation) and interventional (ie, embolization of vascular malformation) approaches or a combination of both. Lately, pharmacologically targeted therapies to inhibit the phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway have been shown to be efficient and safe in reducing overgrowth in patients with PROS.[9] However, they are associated with an impairment of the immune system and have hematologic, metabolic and gastrointestinal side effects.[10]

In the present study, we evaluated the efficacy and safety of current overgrowth treatment modalities for patients with PROS by performing a systematic review of the current literature. We included randomized controlled trials (RCTs), cohort studies, cross-sectional studies, case control studies, and case series with ≥10 patients.[11,12]

METHODS

The present systematic review was conducted in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2020 statement guidelines.

Literature search. A professional medical information specialist (W.M.B.) developed a systematic search strategy to identify data concerning therapy regimens in PROS, which was updated by a second professional medical information specialist (B.M.). EMBASE, MEDLINE (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Google Scholar were last searched on February 13, 2021. The aims of the search were to identify all studies of original research data from human studies on the treatment (including all treatment modalities; eg, surgical, pharmacological, or other) of PROS. The full search strategies for all the databases are provided in the Appendix.

The study protocol was registered on PROSPERO (PROSPERO 2020 CRD42020185010) before the beginning of data extraction. No approval from the local ethics committee was required, because our study was a systematic review of previously reported data via the stated databases.

Selection of included studies. The references were imported using EndNote, and duplicates were removed using the method described by Bramer et al.[13] Using Endnote with the method reported by Bramer et al,[14] two reviewers independently screened titles and abstracts for eligibility. In the case of disagreement on the inclusion of an abstract, a third author made the final decision for inclusion. Likewise, eligible full-texts were assessed by two reviewers independently, with the third author providing the final decision in case of disagreement.

Inclusion and exclusion criteria. Other than prespecified in the PROSPERO protocol, we decided to include only studies that had encompassed a definite reduction of overgrowth of one or more parts of the body. Studies were included if they (1) were cross-sectional, prospective, RCT, or case series of ≥10 patients; (2) included PROS patients diagnosed genetically or clinically; (3) had investigated a medical, surgical, or interventional treatment aimed at reducing hypertrophy; and (4) had collected information on efficacy and safety outcomes. Efficacy outcomes included the extent of overgrowth defined by imaging studies or the clinical presence before and after therapy and general symptom and pain relief (eg, visual analog scale, Eastern Cooperative Oncology Group, Karnofsky performance scale, quality of life [QOL]), and the safety outcomes included any serious adverse event or side effect reported in association with the treatment.

The exclusion criteria were case reports or case series with <10 patients owing to the very high risk of reporting bias in those study types,[12,15] non–English and non–German language studies, studies that had not performed any treatment, and guideline and overview studies without original research data. If full texts could not be found online but were potentially eligible based on the title and abstract, the corresponding authors were contacted directly. Studies were excluded when they were not accessible even via document delivery services. Older studies were excluded if both reviewers agreed independently that the study provided definitions of PROS that were no longer up to date, according to the current International Society for the Study of Vascular Anomalies classification and thus were potentially not representative of the populations of interest in our review (eg, KTS vs Klippel-Trenaunay-Weber syndrome).

The corresponding authors of the reports that had included PROS patients in the study population (eg low flow venous malformations, including patients with KTS)

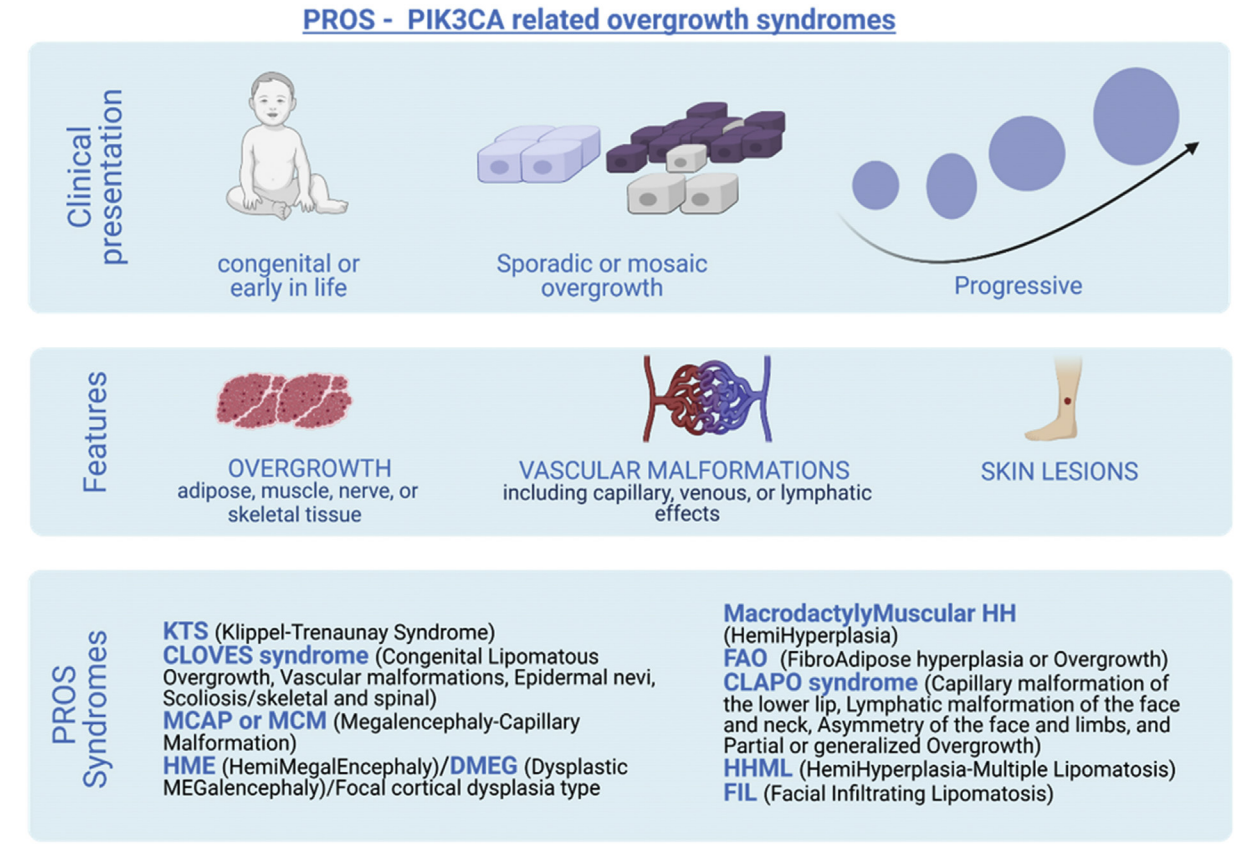

Fig 1. Overview of the most common clinical presentations, features, and PIK3CA (activating mutations of the p110α subunit of phosphatidylinositol 3-kinases)-related overgrowth syndrome (PROS) syndromes. Created with BioRender (available at: biorender.com).

but had not reported the outcome stratified for the subgroup of interest (PROS) were contacted via e-mail and asked for additional specific outcome data on the PROS patients. If such information was not provided within 1 month, the study was excluded.

Data extraction of included studies. Studies were evaluated according to their described treatment modality in the pharmacologic, surgical, or interventional categories. The extracted data included study type, PROS type studied, the overgrowth-affected body area, symptoms that had led to the described treatment, treatment details, and outcome data (ie, improvement or worsening of signs and symptoms, number of interventions, length of follow-up, assessment of outcome [eg, radiologic imaging, self-report, clinical judgment of treating physician]). Finally, any reported safety aspects of the treatment were extracted.

Assessment of risk of bias. To assess the risk of bias (RoB), we used the Newcastle-Ottawa scale (NOS) for cohort studies[16] as prespecified, assessed by two reviewers independently. The RoB was considered low if the NOS score was 8 to 9 stars, moderate for NOS score was 5 to 7 stars, and high if the NOS score was ≤4 stars as recommended by Wells et al.[16] The limitations of this three-dimensional score include assessment of selection of the exposed and unexposed cohort, comparability of the two cohorts, and outcomes assessment.[17,18]

Statistical analysis. Categorical variables are presented as percentages or absolute numbers. Continuous variables are presented as the mean ± standard deviation. Owing to the limited number of studies with data and the heterogeneous definition of the medical input parameters, it was not feasible to pool the results and perform a meta-analysis.

RESULTS

Results from the literature search. The literature search revealed 4592 titles and abstracts. After removing the duplicates, the titles and abstracts of 2787 unique citations were screened, leading to the review of 240 full text reports (Fig 2).

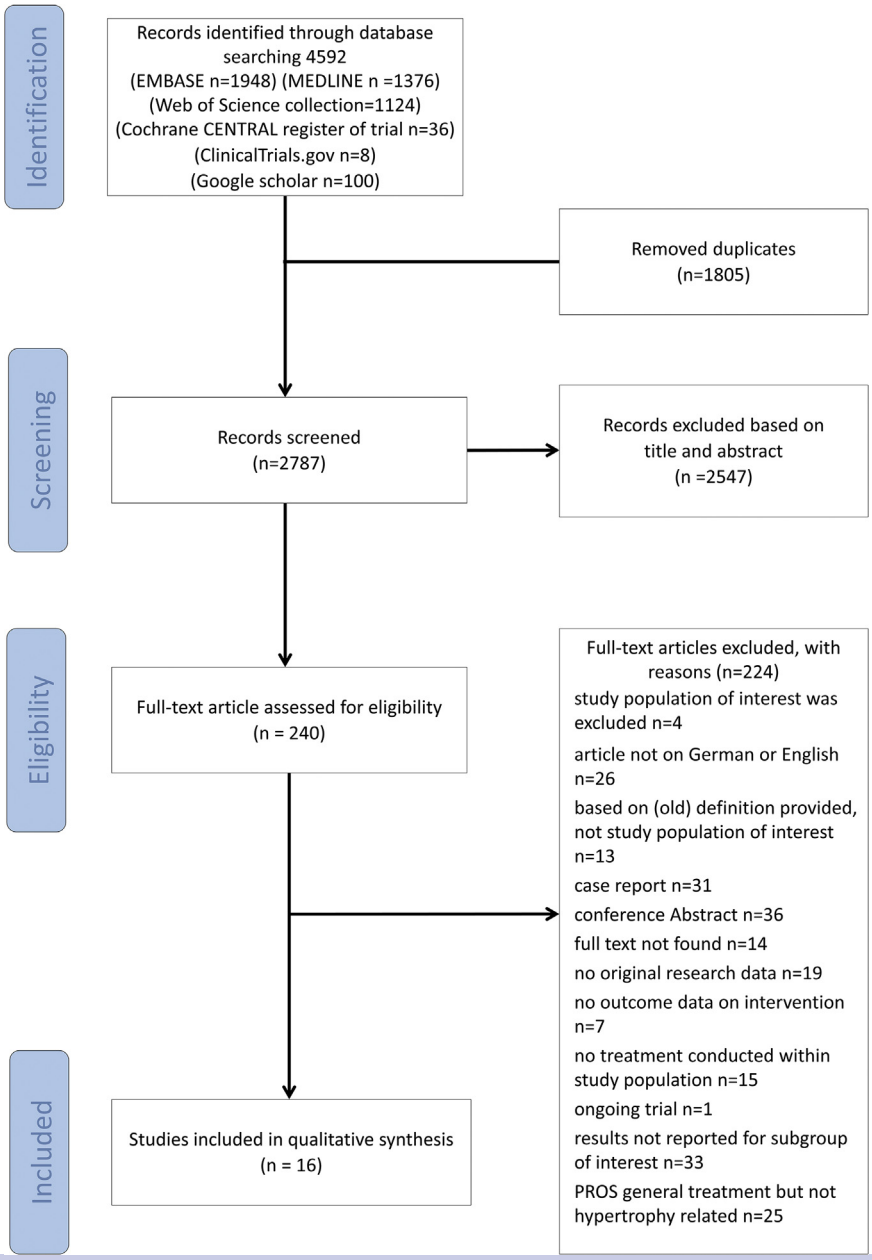

Fig 2. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram for the systematic review of literature.

We had sent an e-mail to 16 authors for additional data on studies to be considered for inclusion. However, no additional data could be collected. Only one study had presented interventional, surgical, and conservative treatment options.[19] Of the 240 studies, 25 had presented interventional treatment methods; however, their aim was mainly to address symptom control and not to assess the reduction of overgrowth. Thus, these were not included in the qualitative analysis. Treatment modalities aimed directly at reducing overgrowth of the affected body part were found in 16 studies, which were included in the final qualitative analysis (Fig 2).

Description of included studies. Of the 16 included studies, overgrowth was treated surgically in 13 (81.3%)[19-31] and pharmacologically in 3 (18.7%).[9,32,33] A total of 351 patients, aged from birth to 83 years, were included and treated for hypertrophy. In three studies (18.7%), the diagnosis of PROS was determined using a genetic (nonclinical) definition for 58 patients. Accordingly, for most of the included studies (81.3%), PROS was defined using the clinical criteria of the associated syndromes and/or radiologic documentation of overgrowth and associated vascular anomalies (Fig 1).

Table I. Risk of bias assessment using Newcastle-Ottawa scale

	Selection					Outcome				
Investigator	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start	Comparability	Assessment	Follow-up sufficient for outcome to occur	Adequacy of follow-up	Total (maximum, 9 stars)	RoB
Venot et al,[33] 2018	*	0	0	*	0	*	*	*	*****	Moderate
Cerrato et al,[21] 2013	*	0	*	*	0	*	*	0	*****	Moderate
Parker et al,[9] 2019	*	0	*	*	0	*	*	*	*****	Moderate
Sandbank et al,[32] 2019	*	0	0	*	0	*	*	*	*****	Moderate
Ishida et al,[27] 1998	*	*	*	*	*	*	*	*	********	Low
Topoleski et al,[26] 1997	*	0	*	*	0	*	*	0	*****	Moderate
Raab et al,[31] 2001	*	*	*	*	*	*	*	*	********	Low
Padwa et al,[30] 2001	0	0	*	*	0	*	*	*	*****	Moderate
Kim et al,[25] 2015	*	*	*	0	*	*	*	0	*******	Moderate
Jacob et al,[19] 1998	*	*	*	0	*	0	*	0	*****	Moderate
Hardwicke et al,[20] 2013	*	*	*	*	**	0	*	0	*******	Moderate
Grogan et al,[24] 1991	*	0	*	*	0	*	0	0	****	High
Chang et al,[22] 2002	*	0	*	*	*	*	*	*	*******	Moderate
Chen et al,[23] 1997	*	0	*	*	0	*	*	0	*****	Moderate
Couto et al,[29] 2015	0	0	*	*	0	*	*	0	****	High
Kotwal et al,[28] 1998	0	0	*	*	0	*	*	*	*****	Moderate

RoB, Risk of bias.
RoB was considered high if ≤4*, moderate 5-7*, low 8-9*. Representativeness of the exposed cohort: * given for truly or somewhat representative of the average individual in the concerned community; Selection of the non-exposed cohort: * given for drawn from the same community as the exposed cohort; Ascertainment of exposure: * given for secure record (eg surgical records) or structured interview; Demonstration that outcome of interest was not present at start of study: * given if yes; Comparability: * given for any factor controlled for and an additional * for any additional factors; Ascertainment of exposure: * given for independent blind assessment or record linkage; Follow-up long enough for outcomes to occur: * given if yes; Adequacy of follow up: * given if complete follow up or subjects lost to follow up unlikely to introduce bias (<5%) or description provided of those lost).

The studies included in the present systematic review included 12 retrospective medical record reviews (75%), one retrospective audit (6.3%; in which outcome data had been collected prospectively after the intervention at a specific follow-up point),[20] and 3 prospective cohort studies (18.7%). The RoB was low for 2 studies (12.5%), moderate for 12 studies (75%), and high for 2 studies (12.5%; Table I).

Surgical studies. The included studies on surgical hypertrophy treatment in PROS (n = 13; 81.25%) were reported from 1991 to 2015.[19-31] The included patients were either pediatric patients only or a mix of pediatric and adult patients. Among the PROS-associated syndromes, most surgical treatment options were described for patients with macrodactyly (nine studies; 69.3%). Five studies had included patients with macrodactyly of the feet[21,22,24-26] and three had included a mix of patients with macrodactyly of the feet and hands.[20,23,28] Ishida et al[27] reported on surgical intervention of the hands only. The characteristics of the included studies are presented in Table II.

Treatment was indicated for patients with macrodactyly who were unable to wear the same-size shoes, those with cosmetic impairment of the lower extremities, and those with functional and cosmetic impairment of the upper extremities. Pain was not reported. Treatment of macrodactyly mainly consisted of debulking and ray resection; however, epiphysiodesis and phalangeal resection were also reported.

In five of nine studies (188 patients, aged from birth to 22 years), more than one operation was performed for most patients, especially those with progressive overgrowth.[20-23,28] The results generally appeared to be better for those with static macrodactyly. The main

Table II. Overview of included studies on surgical treatment

Investigator	Study design	Intervention	Study population	Results	Safety outcomes
Cerrato et al,[21] 2013	Retrospective medical record review	Soft tissue debulking, n = 9; epiphysiodesis, n = 7; ray amputation, n = 6; digit transfer, n = 2; closing wedge osteotomy, n = 11	Macrodactyly, n = 21	Improved function and aesthetics in affected digits in all patients with early soft tissue debulking, osteotomy, and growth arrest by epiphysiodesis	No major complications; hypertrophic scarring, n = 4; decreased sensation, n = 1; flexion contracture, n = 1
Chang et al,[22] 2002	Retrospective medical record review	Toe amputation, n = 6; toe shortening, n = 2; ray resection, n = 3; debulking, n = 3; toe amputation II-III and epiphysiodesis grade I, n = 2	Macrodactyly, n = 17 feet (15 patients)	Painless and able to wear regular shoes, n = 10; painless but necessary to wear a larger shoe, n = 7	Wound healing problems, n = 2; n = 1 necrosis of skin flap
Chen et al,[23] 1997	Retrospective medical record review	Feet: debulking, n = 9; phalangeal resection, n = 5; ray resection, n = 5; interdigitization, n = 1; split-thickness skin graft, n = 1; toe resection, n = 3; epiphysiodesis, n = 1; wedge osteotomy, n = 1; hands: debulking and ray resection, n = 3	Macrodactyly, n = 17 extremities (16 patients)	Feet: operated, n = 8: 5/8 good; 3/8 fair; 0/8 poor; conservative treatment, n = 5: 3/5 fair; 2/5 poor; hands: operated n = 1: 1/1 fair; conservative treatment, n = 2: 2/2 poor	NR
Couto et al,[29] 2015	Retrospective medical record review	Liposuction	Overgrowth treated by liposuction, n = 17	Size reduction with improved function and quality of life (no additional quantitative report), n = 17	No complications
Grogan et al,[24] 1991	Retrospective medical record review	Debulking, n = 11; ray resection, n = 5; phalangeal epiphysiodesis, n = 3; phalangeal resection, n = 4; toe amputation, n = 4; syndactylization, n = 2	Macrodactyly, n = 11 (11 patients; 11 limbs)	Debulking, ray resection, and phalangeal epiphysiodesis worked best for pain-free limbs, equal in length and width; epiphysiodesis progression stopped; amputation alone was not satisfactory; syndactylization created another deformity	Scar formation and persistence of enlarged toes/foot (n = 2); resection of middle phalanx did not produce shortening but a floppy toe that was still broad and long
Hardwicke et al,[20] 2013	Retrospective audit	Surgical vs conservative treatment	Macrodactyly, n = 33 limbs (32 patients)	No significant difference in outcomes (functional, cosmetic, psychosocial) between surgical vs conservative treatment; surgical: "better," n = 30; "same," n = 1; "worse," n = 1	Complications, n = 16 in 66 surgeries: superficial wound infection, n = 9; skin necrosis, n = 2; wound breakdown, n = 2; hypertrophic scarring, n = 2; locking of a joint, n = 1

Table II. Continued.

Investigator	Study design	Intervention	Study population	Results	Safety outcomes
Kim et al,[25] 2015	Prospective cohort study	Ray resection	Macrodactyly, n = 16 patients (18 feet)	Those wearing oversize shoes preoperatively were able to wear normal shoes postoperatively, n = 4; patient wearing preoperative custom-made shoes was able to wear readymade shoes, n = 1; satisfied with outcome, n = 14	Mild discomfort from scar on plantar side of foot
Jacob et al,[19] 1998	Retrospective medical record review	Epiphysiodesis, n = 41; debulking, n = 11; conservative treatment, vascular surgery (eg, reconstruction of deep vein system, stripping)	KTS, n = 252 patients	Ligation and stripping: better, 40%; worse, 25%; same, 35%; excision of vascular malformation: better, 55%; worse, 15%, same, 30%; epiphysiodesis: better, 80%; same, 8%; worse, 10%; no information, 10%; debulking: better, 65%; worse, 15%; same 20%	Death, n = 3 (1%): 1 of cachexia due to massive malformations; 1 of PE after debulking; 1 of nonhealing wounds in lymphedema; overgrowth of normal leg after epiphysiodesis, n = 1; increased symptoms after stripping of veins due to atretic deep femoral vein, n = 1
Padwa et al,[30] 2001	Retrospective medical record review	Patients, n = 10/13: resection of mucosal neuromas, n = 2; debulking, n = 6; osseous reduction of maxilla, n = 3	Facial infiltrating lipomatosis, n = 13 patients	Little change of contour in 5/6 patients after debulking with or without osseous reduction; excised mucosal neuromas did not recur	Three oldest patients developed orbital elevation
Ishida et al,[27] 1998	Retrospective medical record review	Debulking, n = 20; resection of hypertrophic nerve, n = 14; osteotomy, n = 10; epiphysiodesis, n = 4; arthroplasty, n = 3; carpal tunnel release, n = 2; amputation, n = 10	Macrodactyly, n = 28 patients	Affected digits after surgery: length 102% of contralateral side, circumference 121% proximal, 124% distal interphalangeal joints; range of motion: 65° MCP joint; 57° PIP joint; 37° DIP joint; excision of nerves: 4/14 needed further surgery; epiphysiodesis: 4/4 needed no further surgery	Early degenerative changes, n = 3; diminished two-point discrimination after excision of hypertrophic nerves, n = 2
Kotwal et al,[28] 1998	Retrospective medical record review	First-stage defatting, n = 23; second-stage defatting, n = 18; finger shortening, n = 18 (2 with redo); syndactyly release, n = 2; ray amputation, n = 2	Macrodactyly, n = 23	Volume reduction in operated digits: good (reduction of digit ≤50%), n = 12; satisfactory (reduction 25%-50%), n = 7; poor (cosmetically unacceptable, requiring amputation), n = 2	Corrective osteotomy for angular deformity due to lateral scar contraction, n = 3; skin flap necrosis, n = 2

(Continued on next page)

Table II. Continued.

Investigator	Study design	Intervention	Study population	Results	Safety outcomes
Raab et al,[31] 2001	Retrospective medical record review	Blount epiphyseal stapling	Blount epiphyseal stapling, n = 48 patients; 7 with KTS	Leg length difference, −0.71; angle not reported for KTS subgroup	Swelling and wound healing not reported for subgroup of interest; no infections or sensorimotor deficits; loosening or dislocation of staples, n = 4
Topoleski et al,[26] 1997	Retrospective medical record review	Proximal phalangeal epiphysiodesis	Macrodactyly, n = 11 toes (9 patients)	Metaphyseal/diaphyseal width Ratio did not change in all digits; normal proportional growth after surgery, n = 9/11; continued growth of phalanx, n = 2/11	Partial epiphysiodesis with abnormal appearance of metaphyseal contour, n = 1; angular deformity in 30° valgus at MTP of affected toe, n = 1

DIP, Distal interphalangeal; *KTS,* Klippel-Trenaunay syndrome; *MCP,* metacarpophalangeal; *MTP,* metatarsophalangeal; *NR,* not reported; *PIP,* proximal interphalangeal.

reported safety outcomes included hypertrophic scarring and prolonged wound healing.

Two studies reported surgery for patients with KTS to treat leg length differences with epiphysiodesis (n = 46 patients).[19,31] One study reported improvement in 80% of the cases (n = 41 patients).[19] The other study reported a postoperative leg length difference of <2 cm in two of five cases and contralateral overgrowth of 2 to 5 cm in three of five KTS patients. The reported complications included loosening of epiphyseal staples, wound healing problems, and overcorrection with consecutive longitudinal undergrowth of the treated leg.

Couto et al[29] reported liposuction of the hypertrophic parts of the body (trunk, upper and lower extremities, face) in different PROS entities (17 patients; aged 2-34 years) reducing the size, with improved function and QOL in all patients and no further side effects. Padwa and Mulliken[30] reported surgical resection of hypertrophic facial anomalies in 13 patients with fibroadipose overgrowth (age, 1-22 years). However, little to no benefit was found in the correction of facial asymmetry and recurring hypertrophy after follow-up. In 3 patients, an elevation of the ipsilateral eye socket occurred as a complication of surgery.[30] Because of the retrospective study design, 12 of the 13 studies did not report prespecified safety outcomes. An overview of included studies on surgical treatment for PROS is presented in Table II.

Pharmacologic studies. All three studies reporting on pharmacologic interventions included patients with genetic data on *PIK3CA* mutations. PROS patients included those who had presented with syndromic mosaic mutations in the context of CLOVES, KTS, megalencephaly-capillary malformation, and localized overgrowth syndromes involving different parts of the body.

Parker et al[9] and Sandbank et al[32] reported on the use of sirolimus (rapamycin), an mTOR inhibitor with a macrolide structure that is given either orally or topically. The patients had presented with hypertrophy of one or more parts of the body. None of the patients had presented with isolated hypertrophy but had presented with more syndromic characteristics with symptoms and signs of pain, bleeding, and localized intravascular coagulation at baseline. Parker et al[9] reported a significant reduction in the overgrown target lesions (−7.2% ± 16.0%; $P = .04$) after 26 weeks of systemic sirolimus therapy with a target level of 2 to 6 ng/mL. However, no significant improvement in QOL occurred in their 39 patients (age, 3-48 years). Sandbank et al[32] reported on seven patients with PROS within their study population (36.8%). Of the seven patients, six been treated with oral (two patients with CLOVES and four patients with KTS) and one patient with KTS had been treated with topical sirolimus. They reported near complete resolution of cystic hemolymphatic malformations of the chest wall and limb overgrowth in one patient with CLOVES (14.3%) after 22 months of sirolimus treatment. One patient (14.3%) did not respond to treatment, and five patients (71.4%) experienced partial resolution of their baseline symptoms, including the KTS patient with topical sirolimus treatment.

Adverse events occurred in 4 of 7 patients (57%)[32] and 28 of 39 patients (72%),[9] respectively. The incidence of serious adverse events (SAEs) was 21%.[9] These included bacterial and/or viral infections, blood count disorders, elevated liver enzymes, and pulmonary embolism in one patient reported by Parker et al.[9] In the study

Table III. Overview of included studies of medical treatment

Investigator	Study design	Intervention	Study population	Outcome	Results	Safety outcomes
Parker et al,[9] 2019	Prospective cohort study	Oral sirolimus	PROS (CLOVES) and progressive overgrowth and mosaic *PIK3CA* mutation, n = 39 patients	Percentage of change in volume of measured affected and unaffected areas for treated and untreated periods	Significant reduction in volume, −7.2% ± 16.0%; *P* = .04	Withdrew because of AEs, n = 7; 72% had ≥1 AEs related to sirolimus; 21% SAEs; 41% infection; 21% blood or lymphatic disorders; no change in lipid or glucose concentration during treatment period
Sandbank et al,[32] 2019	Retrospective medical record review	Oral or topic sirolimus	Complex vascular anomalies, n = 19 patients (7 with PROS, including KTS and CLOVES)	Stabilization or decrease in lesion size, overgrowth or malformation, weeping/ bleeding, pain, infection, and functional impairment	Near complete resolution, n = 1; partial response, n = 5; no response, n = 1	No side effects, n = 3/7; hypertriglyceridemia, n = 2 (grade I, n = 1; grade III, n = 1); increased ALT (grade I), n = 1; abdominal pain, nausea, n = 1; thrombocytosis, n = 1
Venot et al,[33] 2018	Prospective cohort study	Daily oral alpesilib (BYL719)	*PIK3CA* mutation (all overgrowth syndromes), n = 17 patients	Size of target lesion after treatment, subjective signs and symptoms	Decreased circumference of target lesion: 12.6% ± 3.8% after 3 months; 16.3% ± 3.9% after 6 months; radiologic decrease: 27.2% ± 14.6% after 3 months; 37.8% ± 16.3% after 6 months; improvement of subjective signs and symptoms, all patients	Oral ulceration (grade I), n = 3; transient hyperglycemia (dietary control), n = 1; required more antidiabetic medication, n = 1 (diabetic)

AEs, Adverse effects; *ALT,* alanine aminotransferase; *CLOVES,* congenital lipomatous overgrowth, vascular malformations, epidermal nevi and spinal abnormalities; *KTS,* Klippel-Trenaunay syndrome; *PROS,* PIK3CA (activating mutations of the p110α subunit of phosphatidylinositol 3-kinases)-related overgrowth spectrum; *SAEs,* serious adverse effects.

subgroup reported by Sandbank et al,[32] only mild side effects had occurred (Table III). The reported side effects included infection, hypercholesterolemia, liver enzyme elevation, mouth sores, thrombocytopenia, neutropenia, interstitial pneumonitis, hypersensitivity syndrome, prolonged fever, and abdominal pain.

The third study, by Venot et al,[33] reported the use of alpelisib (BYL179) in a cohort of 17 patients with PROS. A response to treatment was noted in 100% of the treated patients. The mean circumference reduction was 12.6% ± 3.8% and 16.3% ± 3.9% after 3 and 6 months of treatment, respectively. The patients had received an initial dose of 50 to 250 mg once daily, without any details on dose adjustments. Side effects occurred in 29.4% of patients, with only mild adverse events and no serious adverse events were reported. An overview of the included studies on pharmacological treatment, outcomes, and side effects in PROS is presented in Table III.

DISCUSSION

In the present systematic review, we identified 16 studies reporting treatment to reduce overgrowth and hypertrophy in patients with PROS. Our main findings were, first, that therapy regimens with the aim to reduce hypertrophy in PROS are mostly surgical, with the results limited to local outcomes. Second, promising results have been shown with pharmacologic PIK3CA inhibition. However, the existing evidence for the treatment of PROS is limited, and considerable RoB was present. Finally, PROS was defined by a *PIK3CA* gene mutation in only 18.7% of the included studies.

Surgical approaches seem beneficial for patients with macrodactyly. However, as reported by Padwa and

Mulliken,[30] surgery does not seem to be effective for patients with fibroadipose overgrowth, both (macrodactyly and fibroadipose overgrowth) clinically categorized as PIK3CA associated overgrowth syndromes. No data concerning surgical treatment on other PROS types have been reported other than in the form of case reports or small case series (and were, thus, excluded from the present review). Additionally, patients with stable, nonprogressive (static) macrodactyly were included in addition to those presenting with progressive macrodactyly. To the best of our knowledge, the underlying mechanism between static and progressive macrodactyly is not well understood.

Kuentz et al[34] were able to show that in 66.7% of isolated and syndromic overgrowth presentations, a pathogenic PIK3CA mutation was found using next generation sequencing, with a greater prevalence in those with syndromic overgrowth (74.0%) compared with those with isolated overgrowth (35.5%). Therefore, no clear statement concerning surgical therapy for PIK3CA-associated overgrowth identified via *PIK3CA* mutations is possible from the present data, because the disease was diagnosed using clinical judgment alone.

Three trials provided data on targeted therapies (PIK3CA inhibition with oral or topical sirolimus and alpelisib). Sirolimus in the context of vascular anomalies has been used with target plasma concentrations of 10.0 to 15.0 ng/mL, considered "high dose,"[35] and 2 to 5 ng/mL, considered "low dose."[9] The current practice is to start with a "low dose," although this has not been included in a guideline. More difficult has been to propose the optimal duration for this experimental therapy, especially if the patient experiences a response. In such cases, sirolimus can be administered without a time limitation. However, to the best of our knowledge, data on the long-term effects and toxicity are missing. The included studies, however, also did not provide any information regarding the decision to use oral vs topical therapy. Individually targeted therapy based on the identification of tumor oncogenes is an established treatment option to reduce tumor growth. Therapy targeting the expression of genetic variants is effective, not only in the treatment of vascular tumors,[36] but could also become an option for patients with congenital vascular malformations and PROS.[10,37] Identifying the mosaic mutation in PROS patients has been difficult in the past because polymerase chain reaction or Sanger sequencing missed *PIK3CA* mutations owing to the mosaic and low-abundant nature in PROS patients.[38,39] However, with the initiation of next generation sequencing, it became possible to identify mutations with low-level expression of mosaicism variants. Thus, future studies might identify additional mosaic mutations in PROS patients that can aid in targeted therapies.

Implications and future perspectives. The findings from our literature review have revealed the current lack of evidence concerning the reduction of hypertrophy in PROS. However, evidence from prospective cohort studies on the use of repurposed drugs from other indications has suggested that a genetically targeted treatment approach could lead to improvements in the treatment and permanent reduction of hypertrophy in these patients. The diagnosis of PROS should be confirmed by genetic analyses of PIK3CA mutations, among other potential genes, allowing for targeted treatment and improved outcomes for these patients. Ongoing trials testing drugs that target PIK3CA pathways, including sirolimus,[40] ARQ 092,[41] and alpelisib.[42] A trial using taselisib (TOTEM [trial of taselisib in overgrowth]) was recently stopped early for safety reasons after two suspected unexpected serious adverse reactions occurred.[43] Additionally, because PROS is rare, international collaborations are needed to advance the research in this field, to have sufficient numbers of patients in larger, prospective cohort studies and/or RCTs, and to increase support for genetic-based diagnosis and targeted treatments.

Study limitations. The present study was not without limitations. Although our initial aim was to perform a meta-analysis to derive estimates to determine the magnitude and strength of evidence present for the treatment of PROS, a meta-analysis was not feasible owing to insufficient data from the RCTs. Because the terminology for, and definition of, PROS were very inconsistent before the International Society for the Study of Vascular Anomalies definition was established, it was impossible to include studies performed before the 1990s. Because most of the included studies had defined PROS from the clinical findings, it remains unknown how many of the included patients had had a *PIK3CA* mutation, a very important limitation to our review.

Another major problem of the present analysis was the limited data concerning the safety and QOL owing to the mainly retrospective study design without predefined safety assessments. Furthermore, QoL assessments were performed using generic, non–disease-specific QoL instruments, because disease-specific QoL measuring tools for these types of vascular malformations do not exist.

CONCLUSIONS

Surgical options will be beneficial for a specific subgroup of patients with PROS (ie, those with macrodactyly). However, little evidence is available regarding surgery for other PROS entities. Direct PIK3CA inhibition has been emerging as a promising treatment option for PROS patients. However, evidence is missing from randomized controlled trials concerning efficacy and, more

importantly, safety issues. Additionally, a more systematic, genetic definition of PROS using next generation sequencing is needed across populations. International collaborations are also required to address these areas of limited evidence to gather sufficient patient numbers to study these rare diseases.

AUTHOR CONTRIBUTIONS

Conception and design: SB, LA, TM, IB
Analysis and interpretation: SB, LA, DH, YD, JL, TM, JR, IB
Data collection: SB, LA, HA, WB, BM
Writing the article: SB, LA
Critical revision of the article: SB, LA, HA, DH, WB, BM, YD, JL, TM, JR, IB
Final approval of the article: SB, LA, HA, DH, WB, BM, YD, JL, TM, JR, IB
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: IB
SB and LA contributed equally to this article and share co-first authorship.

REFERENCES

1. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet 2012;90:1108-15.
2. Yeung KS, Ip JJ, Chow CP, Kuong EY, Tam PK, Chan GC, et al. Somatic PIK3CA mutations in seven patients with PIK3CA-related overgrowth spectrum. Am J Med Genet A 2017;173:978-84.
3. Lindhurst MJ, Parker VER, Payne F, Sapp JC, Rudge S, Harris J, et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. Nat Genet 2012;44:928-33.
4. Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, Heiberg A, et al. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. Nat Genet 2012;44:941-5.
5. Rios JJ, Paria N, Burns DK, Israel BA, Cornelia R, Wise CA, et al. Somatic gain-of-function mutations in PIK3CA in patients with macrodactyly. Hum Mol Genet 2013;22:444-51.
6. Riviere JB, Mirzaa GM, O'Roak BJ, Beddaoui M, Alcantara D, Conway RL, et al. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. Nat Genet 2012;44:934-40.
7. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, Parker VER, Blumhorst C, Darling T, et al. Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. Am J Med Genet Part A 2014;164:1713-33.
8. Rodriguez-Laguna L, Ibanez K, Gordo G, Garcia-Minaur S, Santos-Simarro F, Agra N, et al. CLAPO syndrome: identification of somatic activating PIK3CA mutations and delineation of the natural history and phenotype. Genet Med 2018;20:882-9.
9. Parker VER, Keppler-Noreuil KM, Faivre L, Luu M, Oden NL, De Silva L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Gen Med 2019;21:1189-98.
10. Keppler-Noreuil KM, Parker VER, Darling TN, Martinez-Agosto JA. Somatic overgrowth disorders of the PI3K/AKT/mTOR pathway and therapeutic strategies. Am J Med Genet C Semin Med Genet 2016;172:402-21.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
12. Katrak P, Bialocerkowski AE, Massy-Westropp N, Kumar S, Grimmer KA. A systematic review of the content of critical appraisal tools. BMC Med Res Method 2004;4:22.
13. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 2016;104:240-3.
14. Bramer WM, Milic J, Mast F. Reviewing retrieved references for inclusion in systematic reviews using EndNote. J Med Libr Assoc 2017;105:84-7.
15. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Med 2018;23:60-3.
16. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 1, 2021.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
18. Hartling L, Milne A, Hamm MP, Vandermeer B, Ansari M, Tsertsvadze A, et al. Testing the Newcastle Ottawa scale showed low reliability between individual reviewers. J Clin Epidemiol 2013;66:982-93.
19. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc 1998;73:28-36.
20. Hardwicke J, Khan MAA, Richards H, Warner RM, Lester R. Macrodactyly—options and outcomes. J Hand Surg Eur 2013;38E:297-303.
21. Cerrato F, Eberlin KR, Waters P, Upton J, Taghinia A, Labow BI. Presentation and treatment of macrodactyly in children. J Hand Surg Am 2013;38:2112-23.
22. Chang CH, Kumar SJ, Riddle EC, Glutting J. Macrodactyly of the foot. J Bone Joint Surg Am 2002;84:1189-94.
23. Chen SH, Huang SC, Wang JH, Wu CT. Macrodactyly of the feet and hands. J Formos Med Assoc 1997;96:901-7.
24. Grogan DP, Bernstein RM, Habal MB, Ogden JA. Congenital lipofibromatosis associated with macrodactyly of the foot. Foot Ankle 1991;12:40-6.
25. Kim J, Park JW, Hong SW, Jeong JY, Gong HS, Baek GH. Ray amputation for the treatment of foot macrodactyly in children. Bone Joint J 2015;97-B:1364-9.
26. Topoleski TA, Ganel A, Grogan DP. Effect of proximal phalangeal epiphysiodesis in the treatment of macrodactyly. Foot Ankle Int 1997;18:500-3.
27. Ishida O, Ikuta Y. Long-term results of surgical treatment for macrodactyly of the hand. Plast Reconstr Surg 1998;102:1586-90.
28. Kotwal PP, Farooque M. Macrodactyly. J Bone Joint Surg Br 1998;80:651-3.
29. Couto JA, Maclellan RA, Greene AK. Management of vascular anomalies and related conditions using suction-assisted tissue removal. Plast Reconstr Surg 2015;136:511e-4e.
30. Padwa BL, Mulliken JB. Facial infiltrating lipomatosis. Plast Reconstr Surg 2001;108:1544-54.
31. Raab P, Wild A, Seller K, Krauspe R. Correction of length discrepancies and angular deformities of the leg by Blount's epiphyseal stapling. Eur J Pediatr 2001;160:668-74.
32. Sandbank S, Molho-Pessach V, Farkas A, Barzilai A, Greenberger S. Oral and topical sirolimus for vascular anomalies: a multicentre study and review. Acta Derm Venereol 2019;99:990-6.
33. Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature 2018;558:540-6.
34. Kuentz P, St-Onge J, Duffourd Y, Courcet JB, Carmignac V, Jouan T, et al. Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. Genet Med 2017;19:989-97.
35. Adams DM, Trenor CC III, Hammill AM, Vinks AA, Patel MN, Chaudry G, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics 2016;137:e20153257.
36. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al; Sirolimus. for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-51.

37. Freixo C, Ferreira V, Martins J, Almeida R, Caldeira D, Rosa M, et al. Efficacy and safety of sirolimus in the treatment of vascular anomalies: a systematic review. J Vasc Surg 2020;71:318-27.
38. Hucthagowder V, Shenoy A, Corliss M, Vigh-Conrad KA, Storer C, Grange DK, et al. Utility of clinical high-depth next generation sequencing for somatic variant detection in the PIK3CA-related overgrowth spectrum. Clin Genet 2017;91:79-85.
39. Shenoy A, Hucthagowder V, Grange D, Cottrell C. Utility of clinical high-depth next generation sequencing for somatic variant detection: application to PIK3CA variant detection in segmental overgrowth related syndromes. Lab Invest 2015;95:470A.
40. Study of sirolimus therapy for segmental overgrowth caused by somatic PI3K activation. Available at: https://clinicaltrialsgov/ct2/show/NCT02428296. Accessed March 1, 2021.
41. Study of Miransertib (MK-7075) in Participants With PIK3CA-related Overgrowth Spectrum and Proteus Syndrome (MOSAIC). Available at: https://clinicaltrialsgov/ct2/show/NCT03094832. Accessed March 1, 2021.
42. Study assessing the efficacy, safety and PK of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum. Available at: https://clinicaltrials.gov/ct2/show/NCT04589650. Accessed March 1, 2021.
43. Trial of taselisib in overgrowth (TOTEM). Available at: https://clinicaltrialsgov/ct2/show/NCT03290092. Accessed June 22, 2021.

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Additional material for this article may be found online at www.jvsvenous.org.

Search strategy for current treatment modalities in PIK3CA-related overgrowth syndromes

Database for literature search
Embase, Medline, Web of Science Core Collection, Cochrane CENTRAL register of trials
Search criteria
Patients: all patients with PIK3CA (activating mutations of the p110α subunit of phosphatidylinositol 3-kinases)-related overgrowth spectrum (PROS)
Intervention: any of treatment modalities listed:
Pharmacotherapy: mammalian target of rapamycin (mTOR) inhibitors, AKT inhibitors, phosphatidylinositol-3-kinase (PI3K) inhibitors (metformin, aspirin)
Surgery: removal of target lesion, debulking
Intervention: alcohol embolization, sclerotherapy, laser therapy
Control: as provided
Outcome
Efficacy

1. Extension of malformation before and after treatment on vascular imaging or clinical presentation

2. General symptom relief and pain reduction (visual analog scale, Eastern Cooperative Oncology Group, Karnofsky performance scale, quality of life)
Safety

1. Any adverse event, adverse effect, or side effect or serious adverse event, adverse effect or side effect reported in association with treatment

Inclusion criteria
Cross-sectional studies
Cohort studies
Randomized controlled trials
Case-control studies
Exclusion criteria
Case reports

Search results from May 20, 2020

	Results	Results after removal of duplicates
Embase.com	1476	1453
Medline ALL Ovid	852	124
Web of Science Core Collection	776	179
Cochrane CENTRAL registry	16	11
Total	3120	1767

Search results from February 13, 2021

	Results	Results after removal of duplicates
Embase.com	1948	1929
Medline Ovid	1376	466
Web of Science core collection	1124	299
Cochrane CENTRAL registry	36	22
ClinicalTrials.gov for ongoing studies/trials	7	8
Google scholar for gray literature/full text search	100	63
Total	4592	2787

Search strategy
Embase.com, n = 1948
('pik3ca related overgrowth spectrum'/de OR (('pik3ca gene'/de OR 'Pi3K/Akt signaling'/de OR 'phosphatidylinositol 4,5 bisphosphate 3 kinase'/de OR 'phosphatidylinositol 3 kinase'/de) AND ('overgrowth syndrome'/de OR 'congenital blood vessel malformation'/de)) OR (('hemihyperplasia'/de OR 'face'/de OR 'face asymmetry'/de OR 'face tumor'/exp) AND 'lipomatosis'/de) OR 'cloves syndrome'/de OR 'macrodactyly'/de OR ('Alexander disease'/de AND ('capillary malformation'/de OR 'cutis marmorata telangiectatica congenita'/de)) OR 'angioosteohypertrophy syndrome'/de OR (((Fibroadipose OR Fibro-adipose) NEAR/3 (hyperplasia OR overgrowth OR vascul*-anomal*)) OR ((hemihyperplas* OR hemi-hyperplas*) NEAR/3 lipomatosis) OR (Congenital NEAR/3 Lipomat* NEAR/3 Overgrow*) OR (cloves NEAR/3 syndrome*) OR (Vascular NEAR/6 (Nevi OR nevus) NEAR/6 Scoliosis NEAR/6 (Skelet* OR Spin*)) OR macrodactyl* OR ((Facial OR face*) NEAR/6 (infiltrat* OR infuse*) NEAR/6 Lipomatosis) OR (Megalencephal* NEAR/6 capilla* NEAR/3 (congenital* OR malform*)) OR (Dysplast* NEAR/3 Megalencephal*) OR (Klippel NEAR/3 Trenaunay) OR angioosteohypertroph* OR angio-osteohypertroph* OR angioosteohypertroph* OR angio-osteo-hypertroph* OR (hemangiect* NEAR/3 hypertroph*) OR ((pik3ca OR pik3-ca OR pik-3ca OR pik-3-ca OR PI3K OR PI-3K OR PI3-K OR PI-3-K) NEAR/6 (overgrow* OR vessel* OR vascular)) OR fava OR pros-syndrome*):ab,ti) AND ('mammalian target of rapamycin inhibitor'/exp OR 'mammalian target of rapamycin'/exp OR 'protein kinase B inhibitor'/exp OR 'protein kinase B'/exp OR Metformin/de OR 'acetylsalicylic acid'/de OR 'drug therapy'/de OR 'surgery'/de OR 'cytoreductive surgery'/de OR 'artificial

embolization'/exp OR 'sclerotherapy'/exp OR 'low level laser therapy'/de OR (((mtor OR protein-kinase OR akt OR PI3K) NEAR/3 (inhibit* OR inactivat*)) OR rapamycin OR sirolimus OR Metformin* OR acetylsalic* OR aspirin* OR (drug* NEAR/3 therap*) OR Pharmacotherap* OR surger* OR surgical* OR surgeon* OR remov* OR debulk* OR cytoreduct* OR embolizat* OR embolisat* OR sclerotherap* OR laser* OR therap* OR treat* OR intervent*):ab,ti)

Medline Ovid, n = 1376

(((exp Phosphatidylinositol 3-Kinases/) AND (exp Blood Vessels/ab)) OR ((Hemihyperplasia, Isolated.rx. OR exp Face/ OR exp Facial Neoplasms/) AND exp Lipomatosis/) OR Megalodactyly.nm. OR (Alexander Disease/ AND (Capillaries/ab OR Cutis marmorata telangiectatica congenital.rx.)) OR angioosteohypertrophy syndrome/ OR (((Fibroadipose OR Fibro-adipose) ADJ3 (hyperplasia OR overgrowth OR vascul*-anomal*)) OR ((hemihyperplas* OR hemi-hyperplas*) ADJ3 lipomatosis) OR (Congenital ADJ3 Lipomat* ADJ3 Overgrow*) OR (cloves ADJ3 syndrome*) OR (Vascular ADJ6 (Nevi OR nevus) ADJ6 Scoliosis ADJ6 (Skelet* OR Spin*)) OR macrodactyl* OR ((Facial OR face*) ADJ6 (infiltrat* OR infuse*) ADJ6 Lipomatosis) OR (Megalencephal* ADJ6 capilla* ADJ3 (congenital* OR malform*)) OR (Dysplast* ADJ3 Megalencephal*) OR (Klippel ADJ3 Trenaunay) OR angioosteohypertroph* OR angio-osteohypertroph* OR angioosteo-hypertroph* OR angio-osteo-hypertroph* OR (hemangiect* ADJ3 hypertroph*) OR ((pik3ca OR pik3-ca OR pik-3ca OR pik-3-ca OR PI3K OR PI-3K OR PI3-K OR PI-3-K) ADJ6 (overgrow* OR vessel* OR vascular)) OR fava OR pros-syndrome*).ab,ti.) AND (TOR Serine-Threonine Kinases/ OR Proto-Oncogene Proteins c-akt/ OR Metformin/ OR Aspirin/ OR Drug Therapy/ OR Surgical Procedures, Operative/ OR surgery.fs. OR Cytoreduction Surgical Procedures/ OR Embolization, Therapeutic/ OR Sclerotherapy/ OR Low-Level Light Therapy/ OR (((mtor OR protein-kinase OR akt OR PI3K) ADJ3 (inhibit* OR inactivat*)) OR rapamycin OR sirolimus OR Metformin* OR acetylsalic* OR aspirin* OR (drug* ADJ3 therap*) OR Pharmacotherap* OR surger* OR surgical* OR surgeon* OR remov* OR debulk* OR cytoreduct* OR embolizat* OR embolisat* OR sclerotherap* OR laser* OR therap* OR treat* OR intervent*).ab,ti.)

Web of Science core collection, n = 1124

TS=(((((Fibroadipose OR Fibro-adipose) NEAR/2 (hyperplasia OR overgrowth OR vascul*-anomal*)) OR ((hemihyperplas* OR hemi-hyperplas*) NEAR/2 lipomatosis) OR (Congenital NEAR/2 Lipomat* NEAR/2 Overgrow*) OR (cloves NEAR/2 syndrome*) OR (Vascular NEAR/5 (Nevi OR nevus) NEAR/5 Scoliosis NEAR/5 (Skelet* OR Spin*)) OR macrodactyl* OR ((Facial OR face*) NEAR/5 (infiltrat* OR infuse*) NEAR/5 Lipomatosis) OR (Megalencephal* NEAR/5 capilla* NEAR/2 (congenital* OR malform*)) OR (Dysplast* NEAR/2 Megalencephal*) OR (Klippel NEAR/2 Trenaunay) OR angioosteohypertroph* OR angio-osteohypertroph* OR angioosteo-hypertroph* OR angio-osteo-hypertroph* OR (hemangiect* NEAR/2 hypertroph*) OR ((pik3ca OR pik3-ca OR pik-3ca OR pik-3-ca OR PI3K OR PI-3K OR PI3-K OR PI-3-K) NEAR/5 (overgrow* OR vessel* OR vascular)) OR fava OR pros-syndrome*)) AND ((((mtor OR protein-kinase OR akt OR PI3K) NEAR/2 (inhibit* OR inactivat*)) OR rapamycin OR sirolimus OR Metformin* OR acetylsalic* OR aspirin* OR (drug* NEAR/2 therap*) OR Pharmacotherap* OR surger* OR surgical* OR surgeon* OR remov* OR debulk* OR cytoreduct* OR embolizat* OR embolisat* OR sclerotherap* OR laser* OR therap* OR treat* OR intervent*)))

Cochrane Central register of trials, n = 36

((((Fibroadipose OR "Fibro-adipose") NEAR/3 (hyperplasia OR overgrowth OR vascul* NEXT anomal*)) OR ((hemihyperplas* OR hemi-hyperplas*) NEAR/3 (lipomatosis)) OR (Congenital NEAR/3 Lipomat* NEAR/3 Overgrow*) OR (cloves NEAR/3 syndrome*) OR (Vascular NEAR/6 (Nevi OR nevus) NEAR/6 Scoliosis NEAR/6 (Skelet* OR Spin*)) OR macrodactyl* OR ((Facial OR face*) NEAR/6 (infiltrat* OR infuse*) NEAR/6 Lipomatosis) OR (Megalencephal* NEAR/6 capilla* NEAR/3 (congenital* OR malform*)) OR (Dysplast* NEAR/3 Megalencephal*) OR (Klippel NEAR/3 Trenaunay) OR angioosteohypertroph* OR angio-osteohypertroph* OR angioosteo-hypertroph* OR angio-osteo-hypertroph* OR (hemangiect* NEAR/3 hypertroph*) OR ((pik3ca OR "pik3-ca" OR "pik-3ca" OR "pik-3-ca" OR PI3K OR "PI-3K" OR "PI3-K" OR "PI-3-K") NEAR/5 (overgrow* OR vessel* OR vascular)) OR fava OR pros-syndrome*):ab,ti) AND ((((mtor OR protein-kinase OR akt OR PI3K) NEAR/3 (inhibit* OR inactivat*)) OR rapamycin OR sirolimus OR Metformin* OR acetylsalic* OR aspirin* OR (drug* NEAR/3 therap*) OR Pharmacotherap* OR surger* OR surgical* OR surgeon* OR remov* OR debulk* OR cytoreduct* OR embolizat* OR embolisat* OR sclerotherap* OR laser* OR therap* OR treat* OR intervent*):ab,ti)

ClinicalTrials.gov (expert search), n = 8

PIK3CA-related overgrowth spectrum

Google scholar: first 100 results (according to relevance ranking)

"PIK3CA related overgrowth" FAVA "Congenital Lipomatous Overgrowth "CLOVES syndrome" Macrodactyly "Facial Infiltrating Lipomatosis" "Capillary Malformation" "Klippel-Trenaunay" therapy surgery treatment