# Consensus on the diagnosis and treatment of PROS (*PIK3CA*-related overgrowth spectrum)

**Russian Society of Pediatric Oncologists and Hematologists**
**Russian Association of Pediatric Surgeons**
**Association of Medical Geneticists of Russia**

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*PROS (PIK3CA-Related Overgrowth Spectrum) encompasses vascular malformations, lipomatosis and other multiple congenital anomalies resulting from activating somatic mutations in the PIK3CA gene. PROS includes macrodactyly, hemimegalencephaly, muscle hemihypertrophy, facial infiltrating lipomatosis CLOVES, megalencephaly, vascular malformations (capillary, venous, lymphatic, arteriovenous and combined vascular malformations), skin disorders, epidermal nevi, etc.*

*The experts of the Russian Society of Pediatric Oncologists and Hematologists, Russian Association of Pediatric Surgeons and Russian Society of Medical Geneticists developed this consensus statement of diagnostics and treatment of PROS.*

**Key words:** PROS, *PIK3CA* mutation, overgrowth spectrum, CLOVES, CLAPO, Klippel–Trenaunay syndrome, macrodactyly, lipomatosis, vascular malformations, epidermal nevus, alpelisib, sirolimus

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***Authors' contributions***
*The all authors made an equal contribution.*

The *PIK3CA*-related overgrowth spectrum (PROS) is characterized by vascular malformations, lipomatosis, and a variety of other congenital abnormalities caused by somatic mutations in the *PIK3CA* gene. PROS is a syndrome that combines macrodactyly, polydactyly, hemihyperplasia, syndactyly, hallux varus, muscle hemihypertrophy, facial infiltrating lipomatosis, CLOVES syndrome, megalencephaly, vascular malformations (capillary, venous, lymphatic, and arteriovenous malformations and their combinations), skin lesions, epidermal nevi, and other conditions (Fig. 1) [1, 2].

When making a diagnosis, the code of the International Classification of Diseases, 10th revision, Q87.3 "Congenital malformation syndromes involving early overgrowth" should be used. The diagnosis can be supplemented with diagnoses from the Q00–Q99 group, as well as D18 and D18.1 "Lymphangioma, any site".

**Pathogenesis**

Mutations in the *PIK3CA* gene cause hyperactivation of phosphoinositide 3-kinase (PI3K), which regulates cell growth and division. Spontaneous somatic mutations of the *PIK3CA* gene typically occur during the early stages of embryogenesis, from days 20 to 56, and, depending on the time of occurrence, result in the development of foci of hypertrophied tissue growth with varying localization (Fig. 2).

**Molecular genetic diagnosis of PROS**

PROS combines a spectrum of tissue overgrowth syndromes caused by a heterozygous somatic mutation in the *PIK3CA* gene that occurs during embryogenesis (usually between days 20 and 56).

To confirm the diagnosis of PROS, a molecular genetic study of the *PIK3CA* gene is recommended in patients with characteristic clinical manifestations (Table 1).

Mutations in PROS are postzygotic and mosaic. This determines the requirements for analysis and interpretation of its findings; it may be necessary to test several tissues to detect a mutation. When interpreting the data, it is necessary to take into account the mosaicism of the activating *PIK3CA* mutation, i.e., its presence only in a small percentage of cells.

It is important to note that even if pathogenic variants (mutations) in the *PIK3CA* gene are not detected, the clinical diagnosis of PROS can be established. This is due to technical difficulties in identifying mosaic mutations, particularly when the affected focus is not accessible for safe biopsy.

If pathogenic variants (mutations) in the *PIK3CA* gene are not detected, it is recommended to perform differential

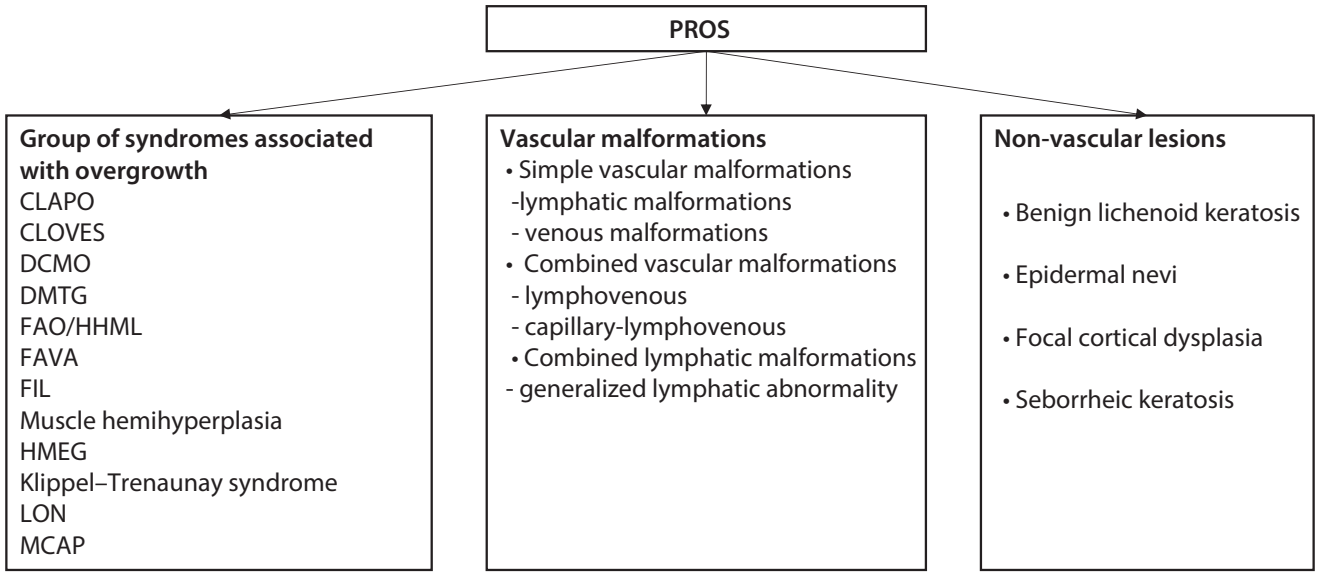



**Fig. 1.** *PROS classification. CLAPO – capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry, and partial/generalized overgrowth; CLOVES – congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies; DCMO – diffuse capillary malformation with overgrowth; DMTG – dysplastic megalencephaly; FAO/HHML – fibroadipose hyperplasia or overgrowth/hemihyperplasia-multiple lipomatosis; FAVA – fibroadipose vascular anomaly; FIL – fibroadipose or infiltrating facial lipomatosis; HMEG – hemimegalencephaly; LON – lipomatosis of the nerve; MCAP – megalencephaly-capillary malformation. Adapted from [2]*

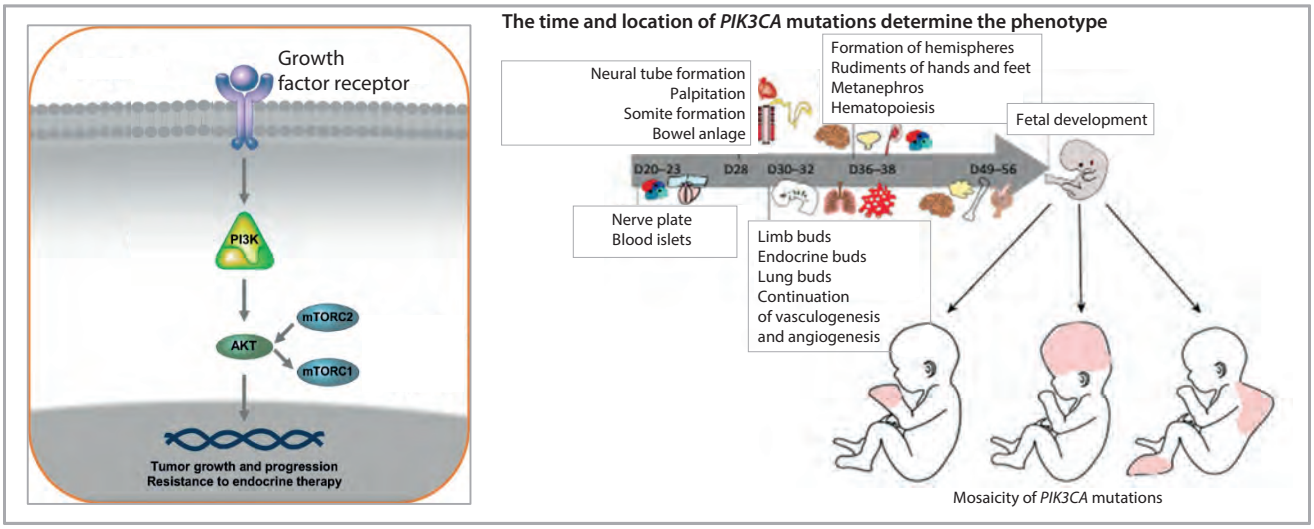



**Fig. 2.** *PROS pathogenesis. Adapted from [3, 4]*

**Table 1.** *Molecular genetic diagnosis of PROS*

| | |
|---|---|
| Material | It is preferable to use tissue biopsy material or post-operative lesion material. It is best to use a biopsy sample of skin taken above the point of tissue overgrowth. Following the biopsy, the material should be immediately immersed in a 10 % solution of neutral buffered formalin, followed by the standard procedure for preparing a paraffin block<br>***Comments.*** The use of liquid biopsy (cell-free fraction of blood, i.e., plasma) is not recommended because it has extremely low sensitivity (information content) in PROS. IntactRNA reagent can be used for fixation. In this case, the samples should be delivered to the laboratory for molecular genetic analysis within 24 hours |
| Method | It is recommended to use NGS (next generation sequencing) with deep coverage to analyze the entire coding region of the *PIK3CA* gene (minimum coverage of each gene region is at least 350×, average coverage is at least 500×)<br>***Comments.*** The use of digital drop PCR (ddPCR) for "hot" codons is permitted as an initial stage, but the results of this method can only be considered if they are positive. A negative result of this test cannot be interpreted and indicates the need for NGS. Exome/genomic sequencing cannot be considered the method of choice for DNA diagnosis of PROS due to the low sequencing depth of individual genes |
| Validation of results | Because some regions of the *PIK3CA* gene contain pseudogenes, it is necessary to provide for the validation of results using an alternative method for rare mutations found in exons 10–14 [5] |
| Interpretation of a negative result | A clinical diagnosis of PROS can also be established if the *PIK3CA* mutation study yields a negative result. This is because mosaic mutations are technically difficult to detect, especially when the affected focus is not accessible for safe biopsy |

diagnosis with Proteus syndrome, tuberous sclerosis, MPPH (megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome), LNSS (linear nevus sebaceous syndrome), SKS (syndrome Smith–Kingmore), basal cell nevus syndrome (Gorlin syndrome), and PTEN harmatoma tumor syndrome (PTHS) [6].

**An interdisciplinary commission comprised of a geneticist, a pediatric oncologist/hematologist, and a surgeon from federal centers makes the decision to establish the diagnosis of PROS in the presence of a specific clinical picture and the absence of mutations in the *PIK3CA* gene.**

### Clinical diagnosis

Clinical signs of PROS include congenital or early onset of segmental/focal overgrowth with or without cellular dysplasia.

Tissue overgrowth foci can be found in the brain, limbs, trunk, and on the face, usually with an asymmetric distribution.

Vascular malformations can be capillary, venous, lymphatic, arterial, or mixed (capillary-lymphatic-venous or arteriovenous). Lymphatic malformations can occur in a variety of locations and result in a variety of clinical manifestations, including swelling, pain, and, in some cases, local bleeding secondary to injury.

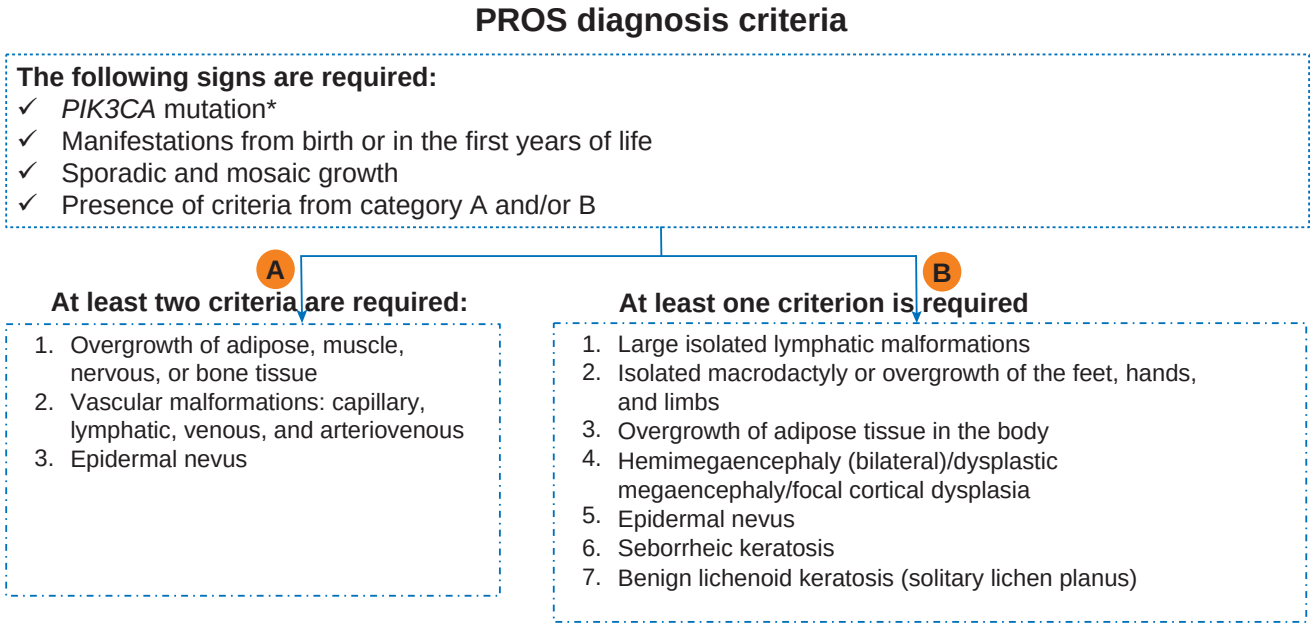
Lipomatous overgrowth can be located ipsilaterally or contralateral to a vascular malformation, if any.

The degree of mental development disorder appears to be related to the presence and severity of seizures, cortical dysplasia (e.g., polymicrogyria), and hydrocephaly.

Endocrine disorders are seen in a few patients. The most common are hypoglycemia (mostly hypoinsulinemic hypoketotic hypoglycemia), hypothyroidism, and growth hormone deficiency.

PROS is diagnosed based on clinical symptoms and the presence of the *PIK3CA* gene mutation (Fig. 3, Tables 2, 3) [7].

**If the *PIK3CA* mutation is not detected, the diagnosis of PROS can be established by a decision of an interdisciplinary commission comprised of a geneticist, a pediatric oncologist/hematologist, and a surgeon from federal centers.**




** – if the PIK3CA mutation study yields a negative result, the diagnosis of PROS can be established by a decision of an interdisciplinary commission comprised of a geneticist, a pediatric oncologist/hematologist, and a surgeon from federal centers.*

**Table 2.** *Manifestations of an isolated form of PROS*

| Organ | Phenotype | Comment |
|---|---|---|
| Brain/head | Hemimegalencephaly, cerebral dysplasia | Cognitive and developmental disorders<br>Facial asymmetry<br>Seizures<br>Focal neurological disorders |
| | Focal cortical dysplasia | Types I, II, III<br>Overgrowth is less pronounced than in hemimegalencephaly<br>Epilepsy uncontrolled by drugs<br>Cognitive impairmen |
| | Focal brain overgrowth with cortical dysplasia; cortical dysplasia can be bilateral | Developmental delay<br>Severe epilepsy in the first few months of life<br>Focal neurological disorders |
| | Facial infiltrating lipomatosis | Unilateral hypertrophy of the soft tissues of the face (most often the cheeks) with fatty infiltration<br>Bone hypertrophy |
| Lymphatic tissue | Isolated lymphatic malformations: dilated vascular channels lined with lymphatic endothelial cells | Fluid cysts usually grow in proportion to the growth of the patient; there may be pain and/or soreness if they are infiltrative |
| Vascular tissue | Vascular malformations | Capillary, venous, or mixed malformations |
| Skin | Vascular malformations<br>Benign lichenoid keratosis<br>Epidermal nevi<br>Seborrheic keratosis | Skin lesions, usually benign |

**Surgical treatment of PROS**

The decision-making algorithm and surgical treatment options for PROS are shown in Fig. 4 and 5.

**Systemic PROS therapy**

1. Systemic drug therapy of PROS is recommended for patients with severe PROS:

- severe pain syndrome or
- symptoms of the disease that disrupt daily life or cause a pronounced cosmetic defect, or pose the threat of similar symptoms/defects against the backdrop of the lesions' ongoing growth in size, provided that these lesions cannot be removed by low-traumatic surgery with satisfactory functional outcomes.

2. Systemic drug therapy should be continued until it no longer works or until intolerable toxicity develops.

***Comment.*** Systemic therapy can be discontinued if the initial manifestations were inoperable, but decreased during the therapy and can be removed with little trauma and with good functional outcomes.

3. It is recommended to use the PI3K inhibitor alpelisib (film-coated tablets) as the drug of choice for systemic drug therapy. It should be administered orally with food in the following regimen [8–11]:

**Table 3.** *Syndromic PROS phenotypes*

| Phenotype | Overgrowth type | Malformations/abnormalities | | | |
|---|---|---|---|---|---|
| | | *cutaneous and vascular* | *musculoskeletal* | *visceral* | *neurological* |
| CLOVES | Asymmetric<br>Congenital lipomatous overgrowth of the limbs or trunk, arms and/or legs<br>Plantar-palmar overgrowth | Low lymphatic flow in areas of overgrowth<br>Linear epidermal nevus<br>Painful paraspinal lesions with high flow and varicose veins | Scoliosis<br>Spina bifida<br>Chest deformation<br>Hallux varus<br>Splayed toes<br>Macro-, poly-, and syndactyly<br>Dislocated knees | Agenesis/ hypoplasia of the kidneys<br>Spleen involvement<br>Nephroblastoma | Hemimegalencephaly, cerebral dysplasia<br>Seizures |
| CLAPO | Partial/generalized lesion of soft tissues and bones | Capillary malformation of the lower lip without progression<br>Lymphatic malformation of the face/neck and upper body | | | |
| FH or FAO | Segmental and progressive overgrowth of subcutaneous and visceral fibrous tissue<br>Skeletal overgrowth<br>Disproportionate linear overgrowth | Vascular malformation<br>Epidermal nevi | Progressive overgrowth of the skeleton (preserved architecture)<br>Polydactyly<br>Lipomatous muscle infiltration | Testicular or epididymis cysts and hydrocephaly<br>Overgrowth of internal organs, except for spleen/ thymus | |
| HHML | Asymmetric overgrowth of a body part or body segment<br>The overgrowth can be static or moderately progressive | Multiple lipomas | | | |
| KTS | Unilateral overgrowth of bones and/or soft tissues of the limb | Venous or lymphatic malformations with low blood flow<br>Portwine stain (capillary malformations) | | | |
| MCAP or M-CM | Megalencephaly and HMEG<br>Generalized overgrowth (macrosomia) | Cutaneous vascular malformations, often "marbled skin" and capillary malformations of the face | Cutaneous syndactyly and postaxial polydactyly or polysyndactyly<br>Subcutaneous lipomas | Nephroblastoma (rare) | Seizures<br>Hypotension<br>Autistic traits<br>Mild to severe mental development disorder<br>Behavioral problems<br>Meningioma symptoms (rare) |

**Note.** *KTS – Klippel–Trenaunay syndrome; M-CM – megalencephaly-capillary malformation.*

- children under 2 years of age: 50 mg once every 2 days;
- children aged 2–6 years: 50 mg once daily;
- children aged 6–18 years: 50 mg once daily, with the possibility of increasing the dose to 125 mg once dailyin case of insufficient effect;
- adults: 30 mg once daily.

***Comments.*** If pathogenic variants (mutations) in the *PIK3CA* gene are not found, it is recommended that the decision to prescribe alpelisib to patients with a clinical picture of PROS be made by an interdisciplinary commission comprised of a geneticist, a pediatric oncologist/hematologist, and a surgeon from federal centers.

If it is impossible to prescribe alpelisib for the treatment of PROS, it is recommended to use an mTOR inhibitor (sirolimus) in the following regimen: 0.8 mg/m2/day orally in 2 doses with an interval of 12 hours [12].

### Monitoring of therapy efficacy

It is recommended to evaluate the efficacy of systemic therapy with alpelisib or sirolimus once every 3–6 months

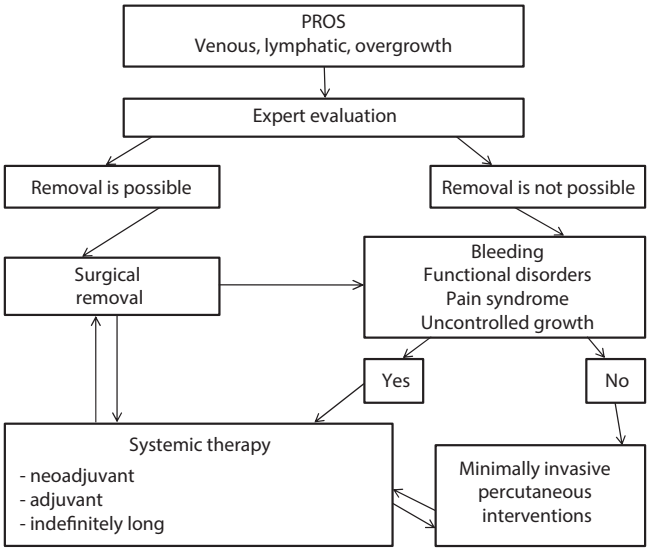



**Fig. 4.** *Algorithm for making a decision on PROS surgical treatment. Minimally invasive percutaneous interventions (microfoam sclerotherapy, microfoam sclerotherapy with subtraction radiography, endovasal laser coagulation, endovasal radiofrequency coagulation, selective photothermolysis, photocoagulation, electrosclerotherapy, and other types of destruction)*

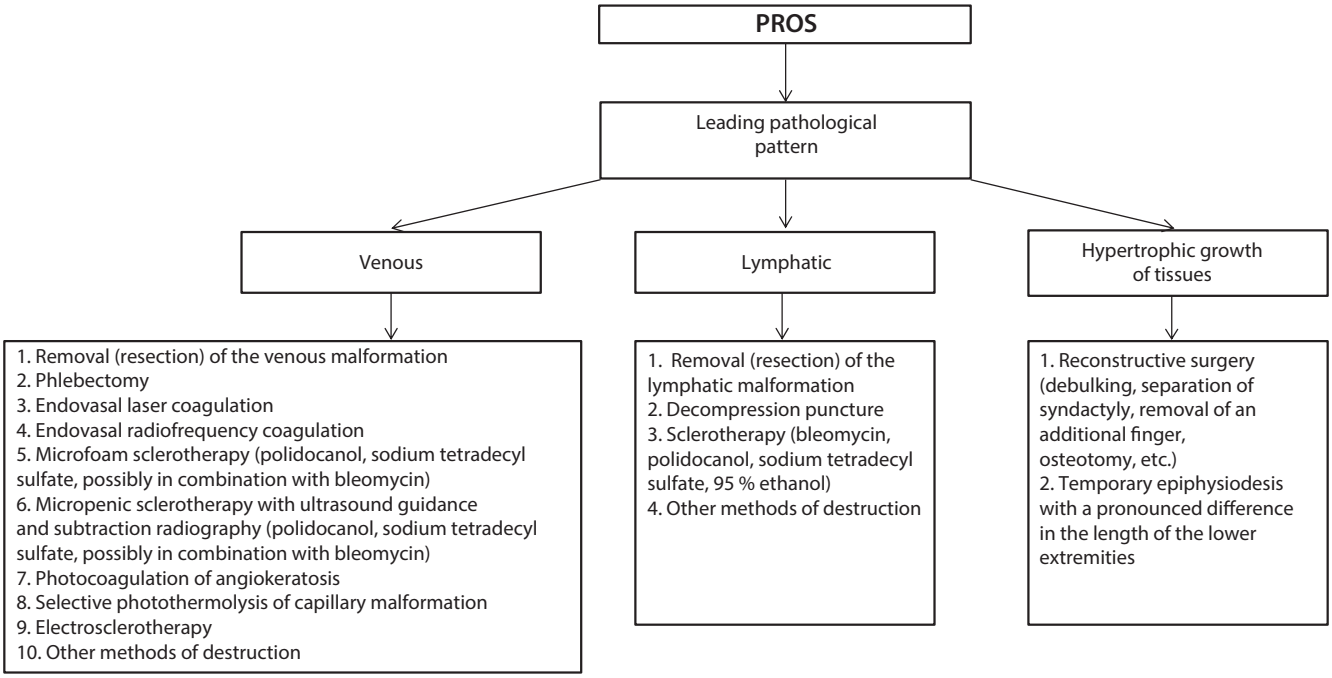



**Fig. 5.** *Possibilities of surgical treatment depending on the leading pathological pattern*

using X-ray examination, MRI, and CT to assess the size of the lesions.

It is recommended to evaluate the effectiveness of surgical and minimally invasive treatment once every 3–6 months. If a relapse of the disease or recurrence of clinical symptoms is detected following surgical or minimally invasive treatment, it is recommended to perform expert evaluation to decide whether to pursue further surgical or minimally invasive treatment or systemic therapy.

It is recommended to evaluate subjective symptoms (pain, weakness) using a visual analogue scale.

A satisfactory outcome of systemic therapy and the basis for its continuation is stabilization or improvement of the condition (decrease in the size of foci, reduction in pain, etc.).

**Contacts of centers for consultation of patients with PROS**

Molecular genetic diagnosis of PROS syndrome in children is performed in the Research Centre for Medical Genetics named after Academician N.P. Bochkov in Moscow and in the N.N. Petrov National Medical Research Center of Oncology, Ministry of Health of Russia in St. Petersburg.

At the Research Centre for Medical Genetics named after Academician N.P. Bochkov, you can book a medical genetic consultation and/or transfer of tissue samples from the lesion by e-mail: semenova@med-gen.ru (geneticist Natalia A. Semenova). Consultation and molecular genetic testing for Russian citizens are free of charge.

To determine the *PIK3CA* gene mutation in St. Petersburg, please contact the Reference Center for Pathomorphological, Immunohistochemical, Molecular Genetic, and Radiation Research Methods of the N.N. Petrov National Medical Research Center of Oncology, Ministry of Health of Russia by phone: +7 (812) 439-95-28 or by e-mail: mol.oncology@gmail.com, to coordinate the arrival of the courier to collect the paraffin block with tissue from the lesion. The study is carried out free of charge as part of the Center's research program. Delivery and return of the tissue sample by courier is free of charge throughout Russia.

***Patients with suspected PROS may be referred to any of the following centers for consultation, diagnosis, and treatment:***

1. Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Ministry of Health of Russia. Through the appointment desk of the Advisory Department, by phone: +7 (495) 287-65-70, you can make an appointment with pediatric oncologists Yulia M. Mareeva and Anastasia S. Salomatina.

Consultation is possible within CHI (referral according to form 057/u). Also, the patient's documents (including visualization in DICOM format) can be sent by e-mail: info.archive@fnkc.ru, with a comment in the subject line: "For Yulia M. Mareeva", or via a secure communication channel at the Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Ministry of Health of Russia, for a telemedicine consultation.

2. Research Institute of Pediatric Oncology and Hematology named after Academician of the Russian Academy of Medical Sciences L.A. Durnov at N.N. Blokhin National Medical Research Centre of Oncology, Ministry of Health of Russia. The Polyclinic Department; the appointment of a pediatric oncologist Selima A. Sardalova is carried out on the day of the visit. You can also send documents by e-mail: orgmetodniidog@ronc.ru, with a comment in the subject line: "For Amina M. Suleymanova" or "For Garik B. Sagoyan".

3. Russian Children's Clinical Hospital of the N.I. Pirogov Russian National Research Medical University, Ministry of Health of Russia. You can book a consultation at Department of X-ray Surgical Methods of Diagnosis and Treatment with Yuri A. Polyaev or Roman V. Garbuzov by phone: +7 (495) 936-90-25.

4. Children's City Clinical Hospital named after N.F. Filatov of Moscow City Health Department. You can book a consultation with Dr. Ruslan A. Khagurov by phone +7 (499) 254-10-10, or via the hospital website: https://filatovmos.ru.

5. Department of Chemotherapy for Hematologic Diseases and Bone Marrow Transplantation for Children of the Almazov National Medical Research Centre, Ministry of Health of Russia. You can contact Yulia V. Dinikina by phone +7 (963) 249-68-52.

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