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Original Article

# Surgical Treatment of Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis Complex Patients

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ABSTRACT

**BACKGROUND:** Subependymal giant cell astrocytoma is a brain tumor associated with tuberous sclerosis complex. There are two treatment options for subependymal giant cell astrocytomas: surgery or mammalian target of rapamycin inhibitor. The analysis of outcome of subependymal giant cell astrocytoma surgery may help characterize the patients who may benefit from pharmacotherapy. **METHODS:** Sixty-four subependymal giant cell astrocytoma surgeries in 57 tuberous sclerosis complex patients with at least a 12-month follow-up were included in the study. The tumor size, age of the patients, mutation in the *TSC1* or *TSC2* gene, indication for the surgery, and postsurgical complications were analyzed. **RESULTS:** The mean age of patients at surgery was 9.7 years. Mean follow-up after surgery was 63.7 months. Thirty-seven (57.8%) tumors were symptomatic and 27 (42.2%) were asymptomatic. Patients with *TSC2* mutations developed subependymal giant cell astrocytoma at a significantly younger age than individuals with *TSC1* mutations. Four patients (6.2% of all surgeries) died after surgery. Surgery-related complications were reported in 0%, 46%, 83%, 81%, and 67% of patients with tumors <2 cm, between 2 and 3 cm, between 3 and 4 cm, >4 cm, and bilateral subependymal giant cell astrocytomas, respectively, and were most common in children younger than 3 years of age. The most common complications included hemiparesis, hydrocephalus, hematoma, and cognitive decline. **CONCLUSIONS:** Our study indicates that subependymal giant cell astrocytoma surgery is associated with significant risk in individuals with bilateral subependymal giant cell astrocytomas, tumors bigger than 2 cm, and in children younger than 3 years of age. Therefore, tuberous sclerosis complex patients should be thoroughly screened for subependymal giant cell astrocytoma growth, and early treatment should be considered in selected patients.

***Keywords:*** subependymal giant cell astrocytoma, tuberous sclerosis complex, outcome, surgery, prognostic factor, mTOR inhibitors
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## Background

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of hamartomas in various tissues.[1] The incidence of TSC has

been estimated as 1 in 6000 live births.[2] TSC is caused by inactivating mutations in either of two genes: *TSC1* or *TSC2*,[2] leading to hyperactivation of mammalian target of rapamycin (mTOR) pathway.[2,3] *TSC1* and *TSC2* mutations account for about 15% to 20% and 65% to 75% of all TSC patients, respectively, and in about 13% of patients no mutation is identified.[4,5]

Subependymal giant cell astrocytoma (SEGA) is a rare low-grade brain tumor representing 1% to 2% of all pediatric brain tumors and occurring almost exclusively in TSC patients.[6] Usually, they grow in children and adolescents,[7,8] and in this age group is the major cause of morbidity and mortality.[9,10] SEGAs are typically located near the foramen of Monro and may cause hydrocephalus (Fig 1A).[6,9]

Recently, it was shown that mTOR inhibitors, rapamycin and its derivate, everolimus, are effective in the treatment of many TSC-related tumors, including SEGA.[11-13] The US Food and Drug Administration and European Medicines Agency approved everolimus to treat patients with SEGA associated with TSC who cannot be curatively treated with surgery.

Surgical resection remains the recommended treatment for SEGA producing clinical symptoms.[14,15] Surgery also remains the standard treatment for SEGAs demonstrating serial growth on neuroimaging, but experts indicate that some patients may benefit more from medical treatment.[15,16] Increasing number of reports show that mTOR inhibitor is safe and effective in TSC patients, even young children, with SEGAs.[11-13,17] Moreover, medical treatment may influence not only the target lesion, but also other TSC-associated symptoms,[12,17,18] thus representing a potentially valuable alternative for elective surgery.

The data on safety and efficacy as well as outcomes of surgical treatment of SEGA are very limited and variable.[19-22] There are no established predictors of prognosis of SEGA surgery, and there is no consensus on the best timing for surgery. There are also no biomarkers to identify the best candidates for pharmacotherapy with mTOR inhibitor or elective surgery.

The aim of this study was to analyze our large cohort of TSC patients who underwent SEGA surgery who were followed at the Children's Memorial Health Institute, Warsaw, to establish the safety and efficacy of surgical treatment of SEGA in TSC patients.

## Materials and Methods

The study was approved by The Children's Memorial Health Institute Ethics Committee. The records of patients with a history of SEGA surgery who were followed at the Department of Neurology and Epileptology, the Children's Memorial Health Institute, Warsaw, between 2000 and 2012 were retrospectively reviewed. The inclusion criteria were histologically proven diagnosis of SEGA, clinically definite TSC based on Roach's criteria,[1] presurgical neuroimaging and surgery report available, and at least a 12-month follow-up after surgery with full neurological examination and brain magnetic resonance imaging/computed tomography performed. The patients who died in the first year after surgery and the relation of death to surgery assessed as probable were also included in the analysis.

The analyzed data included patient demographics; mutational analysis results, if available; the presenting symptoms; size of the tumor; surgical approach and the extent of surgery; any adverse events; results of follow-up neurological examination; and neuroimaging studies. Mutational analysis was performed in either of two laboratories: Genetics Laboratory, Translational Medicine Division, Brigham and Women Hospital, Boston, MA, or the Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff, Great Britain.

Results were analyzed statistically using two-proportion Z-test with significance set at $P \leq 0.05$.

## Results

Fifty-seven patients with a history of SEGA surgery were included in the study. All patients underwent SEGA surgery between 1994 and 2011. Forty-four patients were operated on at the Department of Neurosurgery, The Children's Memorial Health Institute; eight at the Department of Paediatric Neurosurgery, Silesian Medical University; and five in other neurosurgical departments in Poland. Altogether, 64 surgeries were analyzed because seven patients had two separate SEGA surgeries: two because of regrowth of

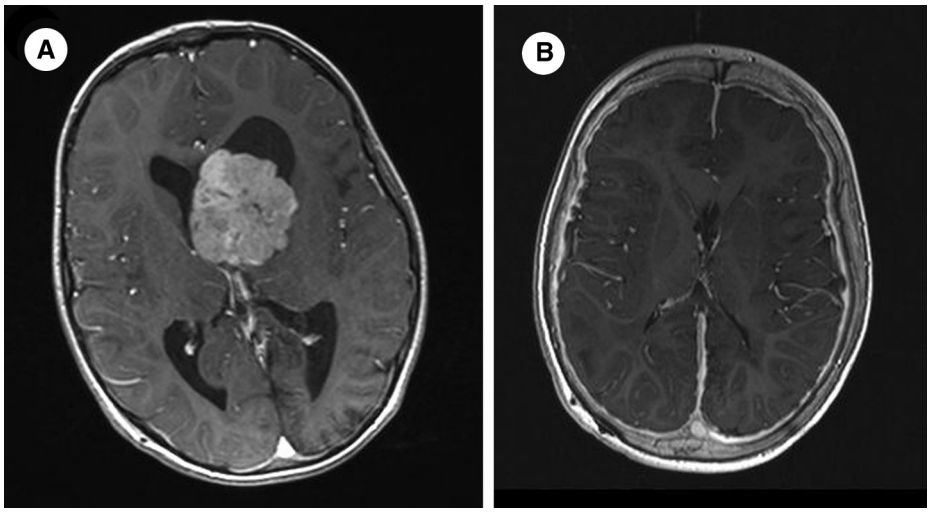


**FIGURE 1.**
Brain magnetic resonance image showing a large subependymal giant cell astrocytoma located near the foramen of Monro and causing hydrocephalus in a tuberous sclerosis complex patient (A). Postsurgery brain magnetic resonance image of the same patient showing complete resection of the tumor (B).

partially removed tumor and five because of new contralateral tumor development.

There were 25 (43.9%) females and 32 (56.1%) males. Mean follow-up was 63.7 months (median 60 months), ranging from 12 to 168 months, with the exception of four patients who died in association with surgery. Three deaths occurred within 7 days after surgery and one 3 months after surgery.

The mean age of the patients at surgery was 9.7 years (range 6 weeks to 26 years). Six (9.4%) patients underwent surgery before the age of 3 years, 31 (48.4%) at between age 3 and 10 years, 23 (35.9%) between age 10 and 16 years, and four (6.2%) at older than age 16 years.

Mutational analysis was performed in 37 patients. The *TSC1* mutation was found in 10 patients (27.0%), *TSC2* mutation in 21 patients (56.7%, including five [13.5%] with a large deletion affecting the *PKD1* gene), and no mutation was identified in six patients (16.2%). The patient age distribution at first SEGA surgery among the patients with *TSC1*, *TSC2*, and *TSC2/PKD1* mutations and patients with no mutation identified is shown in Figure 2. Patients with a *TSC2* mutation required surgery at a younger age (average 6.8 years) than did patients with a *TSC1* mutation (12.9 years, $P = 0.01$) and patients with no mutation identified (11.3 years; $P = 0.02$). Patients with a *TSC2/PKD1* mutation underwent surgery earlier (average age 3.6 years) than did patients with other *TSC2* mutations (average age 7.8 years; $P < 0.05$), a *TSC1* mutation (12.9 years, $P < 0.05$), and patients with no mutation identified (11.3 years; $P < 0.05$).

Thirty-seven (57.8%) tumors were operated on because the patients developed clinical symptoms, and 27 (42.2%) tumors were removed because of documented tumor growth and/or hydrocephalus revealed on neuroimaging. Six patients had shunts implanted before SEGA surgery. In 13 (22.8%) patients, symptomatic SEGA was the first sign of TSC. Two of the patients were infants, and nine were older children with very mild presentations of other symptoms of TSC. In five patients, mutational analysis was undertaken; in three of these patients, it disclosed a *TSC1* mutation, in one patient a *TSC2* mutation, and in one patient no mutation was identified. Symptoms of SEGA included headache, nausea and vomiting, visual disturbances and/or visual loss, hemiparesis, seizures, cognitive functions deterioration, and syncope (Table 1).

The maximum diameter of SEGA was <2 cm in 13 (20%) patients, between 2 and 3 cm in 13 (20%) patients, between 3 and 4 cm in 12 (18.7%) patients, and >4 cm in 26 (40.6%) patients. Nine patients (9/57; 15.8%) presented with bilateral ("mirror") tumors simultaneously and in all of them both tumors were removed at the same surgery.

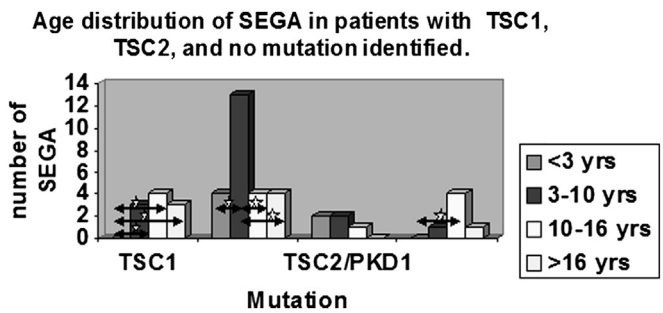


**FIGURE 2.**
Age distribution of subependymal giant cell astrocytoma (SEGA) in patients with mutations in the *TSC1*, *TSC2*, *TSC2/PKD1* genes, and no mutation identified. *$P < 0.05$. TSC, tuberous sclerosis complex.

**TABLE 1.**
Signs and symptoms of subependymal giant cell astrocytoma development in tuberous sclerosis complex patients

| Sign/Symptom | Incidence; n (%) |
|---|---|
| Headache | 29 (43.5) |
| Nausea and/or vomiting | 25 (39) |
| Visual disturbances | 12 (17.7) |
| Hemiparesis | 10 (15.6) |
| New seizures or increased number of seizures | 7 (10.9) |
| Cognitive decline | 4 (6.2) |
| Syncope | 2 (3.1) |

Thirty-seven (57.8%) tumors were removed when clinical symptoms were present.

In 58 (90.6%) tumors, gross total resection (Fig 1B) was performed; no regrowth of tumor was observed in this group. Six tumors (9.4%) were removed subtotally; five (83.3%) of them regrew in 3 to 12 months requiring either second surgery (two SEGAs) or mTOR inhibitor (three patients). One subtotally removed tumor remained stable for 9 years. All partially removed SEGAs exceeded 2 cm in diameter.

In most cases (56 surgeries, 87%) the transcallosal approach was used to remove SEGA. Five tumors (7.8%) were removed via transcortical approach and three (4.7%) via endoscopy.

Surgery-related complications were observed in 37 (57.8%) patients. Some patients suffered from more than one adverse event, and altogether 48 complications were reported. Twenty-seven surgeries were uneventful.

Four patients (6.2% of all surgeries) died within 1 year after surgery. Three patients died within 7 days postoperatively: one because of drug-resistant status epilepticus, one because of massive intracerebral bleeding, and one because of cardiac arrest. One patient died 3 months after partial tumor resection because of tumor regrowth and acute hydrocephalus. The complications observed during the first year postoperatively included hydrocephalus requiring shunt implantation, hemiparesis, intracranial bleeding, cognitive decline, meningitis, diabetes insipidus, seizures, precocious puberty, and neuropathic headache. Most of these complications resolved without sequelae within 1 year. After 12 months, the persistent complications included hemiparesis, cognitive decline, precocious puberty, and neuropathic headache. Table 2 presents the incidence of surgery-related complications. There was statistically significant correlation between the risk of complication and the size of SEGA. Patients operated on for tumors smaller than 2 cm, regardless the presence of symptoms, did not experience any surgery-related complications. Complications were noted in four (30.8%) patients with tumors between 2 and 3 cm in diameter, in eight (66.7%) patients with tumors between 3 and 4 cm, in 19 (73%) patients with tumors bigger than 4 cm, and in six patients (67%) with bilateral SEGAs (Fig 3). Complications were also more frequently seen in young children younger than 3 years of age (in five of six tumors; 83.3%) than in children between 3 and 10 years (in 16 of 31 tumors; 51.6%), children between 10 and 16 years (in 15 of 23 tumors,

**TABLE 2.**
Complications related to surgery in first 12 months and persisting beyond the first year after surgery in tuberous sclerosis complex patients operated on for SEGA

| Complication | Occurrence in 12 Months After Surgery | | Persisting Beyond 12 Months After Surgery | |
|---|---|---|---|---|
| | n | % | n | % |
| Hydrocephalus requiring shunt implantation | 13 | 20.3 | — | — |
| Hemiparesis | 14 | 21.8 | 8 | 12.5 |
| Intracranial bleeding | 9 | 14 | — | — |
| Cognitive decline | 4 | 6.2 | 3 | 4.7 |
| Meningitis | 2 | 3.1 | — | — |
| Diabetes insipidus | 2 | 3.1 | — | — |
| New seizures or increased number of seizures | 2 | 3.1 | | — |
| Precocious puberty | 1 | 1.6 | 1 | 1.6 |
| Neuropathic headache | 1 | 1.6 | 1 | 1.6 |

65.2%) and older patients (in one of four tumors, 25%), but the differences were not statistically significant.

Adverse events were more frequent in patients operated on for symptomatic SEGA (in 26 of 37, 70.2%) than with asymptomatic tumors (9 of 27, 33.3%; $P < 0.05$).

Complications were observed in 33 (58.9%) and 4 (80%) patients operated via transcallosal and transcortical approach, respectively. Patients operated by means of endoscopic approach did not experience complications, but none of them presented with SEGA bigger than 2 cm.

Fifteen patients (26.3%) developed contralateral SEGA in 6 to 120 months after the first surgery and 10 of them required either second surgical intervention (three SEGAs) or treatment with mTOR inhibitor (seven patients).

## Discussion

Recent clinical research that showed efficacy of mTOR inhibitors in the treatment of SEGA associated with TSC has opened a discussion on benefits and risks of SEGA surgery and pharmacological therapy. It has also exposed the urgent need of analyses of surgical treatment outcomes identification of risk factors for poor prognosis associated with surgery. Our cohort of TSC patients operated on for SEGA is the largest published. Moreover, most (77%) of surgeries we analyzed were performed by the same team of neurosurgeons; this significantly reduced the expertise-related bias.[23]

Our study indicates that surgical treatment of SEGA >3 cm is burdened with more than 67% risk of surgery-related complication. Surgery on tumors >4 cm was associated with a 73% risk of adverse events. Bilateral SEGAs, regardless their size, were associated with 67% risk of complications after surgery. In patients undergoing surgery for SEGAs smaller than 2 cm, no complications were observed. This is in accordance with other previous study of Cuccia et al.,[24] who found no significant complications in patients operated on for SEGA smaller than 3 cm. Torres et al.[25] reported that symptomatic SEGA is associated with significantly higher risk of surgery-related complications than asymptomatic tumors removed because of documented growth on serial neuroimaging studies. Currently, brain magnetic resonance imaging or computed tomography is recommended every 2 years in TSC patients,[15,16,23] and early surgery seems to reduce mortality and morbidity related to SEGA.[25,26] However, because the growth rate of SEGAs is highly variable[27] and unpredictable until now, research focused on risk factors for SEGA development and prognostic factors of SEGA growth are urgently needed to identify the patients who may benefit from early surgery and those in whom “watch and wait” approach could be more advantageous.

The surgery-related complications reported in our study included persisting hydrocephalus requiring shunt implantation, focal deficits, intracranial bleeding, cognitive decline, meningitis, diabetes insipidus, and seizures. Most of them were temporary and were not observed beyond 12 months after surgery. However, focal deficits, precocious puberty, and neuropathic headache persisted in some patients for a longer time.

The incidence of surgery-related infections was low (3.1%) in comparison to the data reported by Sun et al.[28]

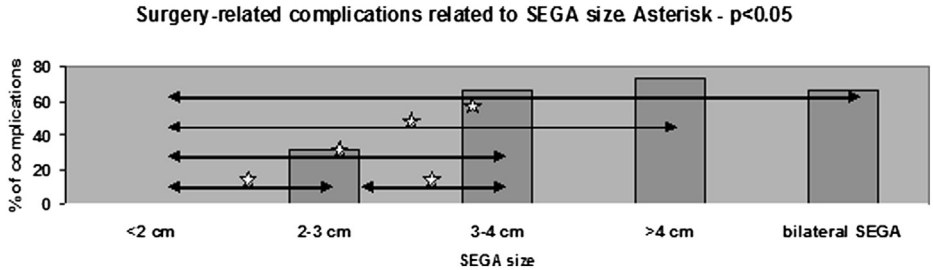


**FIGURE 3.**
Surgery-related complications in patients operated on for subependymal giant cell astrocytoma with maximum diameter >2 cm, 2 to 3 cm, 3 to 4 cm, >4 cm, and bilateral tumors, respectively. *$P < 0.05$. There were no complications observed in patients with tumors smaller than 2 cm.

They reviewed medical data of 47 TSC patients undergoing surgery for SEGA by analyzing three large US national health care claims databases. In their study, during the first postsurgery year, 48.9% of patients developed postoperative complications, including 6.4% of postoperative infections, 17.0% subdural empyemas, and 2.1% epidural abscesses. However, the main limitation of their study is that it was based only on data in a database. The size of SEGA and the surgical approach were not known. Moreover, patients had surgery in many different centers, each likely having different experience in surgery of SEGA.

In our patients with SEGA, *TSC1* mutation was identified in 27% of all patients who underwent mutational analysis. *TSC2* mutation was found in 56.7% of patients. This suggests that SEGAs develop significantly more frequently in individuals with *TSC1* mutations than previously reported (15%).[29,30] In 11 of our patients, symptomatic SEGA was the first symptom of TSC, and among those who had mutational analysis done, the *TSC1* mutation accounted for three of five patients. This might suggest that TSC is misdiagnosed in some patients with a *TSC1* mutation and mild clinical presentation of the disease.

We showed that a *TSC2* mutation is associated with SEGA development at a younger age than with a *TSC1* mutation. Therefore, we recommend more frequent neuroimaging examinations in children with *TSC2* mutations. Large genomic mutations affecting both *TSC2* and *PKD1* genes are rare and account for 2% to 3% of all TSC patients,[31] but in our cohort *TSC2/PKD1* mutations were found in 13.5% of patients. Moreover, in this group of patients, SEGA developed at significantly younger age than in individuals with other *TSC2* or *TSC*1 mutations. The prevalence of SEGA among patients with mutations in *TSC1*, *TSC2*, or *TSC2/PKD1* and the mechanisms underlying the differences in SEGA development risk between the groups requires further studies. Nevertheless, our results indicate that patients with polycystic kidneys should be screened for SEGA from birth.

We observed more surgery-related complications in patients younger than 3 years of age than in older children. Goh et al.[27] reported more complication in patients older than age 11 years; however, they analyzed 11 patients only. Poor outcome in younger children observed in our study may be at least partly associated with more rapid SEGA growth or overall more severe TSC presentation.

The risk of SEGA regrowth in our study was high in patients with partial tumor removal. Partial removal was done only in patients with tumors larger than 2 cm. In all patients in whom gross total SEGA removal was achieved, surgery appeared to be curative. In some individuals with large or bilateral SEGAs, the induction therapy with mTOR inhibitor might enable subsequent complete surgery; however, such an approach requires clinical studies.

Sun et al.[28] reported a high rate of postsurgery diagnosis of SEGA (34%) and a high rate of second SEGA surgery in the first 12 months after first surgery (12%). However, it is not known whether the second diagnosis was because of SEGA regrowth or appearance of a new SEGA. It is also not known what the proportion of gross total and partial first surgeries was. In our cohort, 15 patients (26.3%) developed contralateral SEGA 6 to 120 months after first surgery; 10 of them required either second surgical intervention (three SEGAs) or treatment with mTOR inhibitor (seven patients). Given the frequency of bilateral tumors at first surgery (nine patients, 15.8%), the overall incidence of bilateral SEGA in our study was 42.1%. This is more than reported by Pascual-Castroviejo,[22] and may suggest that some yet unknown factors predispose TSC patients to SEGA development.

In conclusion, we showed that SEGA surgery is safe and effective in patients presenting with tumors smaller than 2 cm. Therefore, periodic brain neuroimaging is recommended for TSC patients to identify growing SEGAs. Patients with *TSC2* mutations, and especially with *TSC2/PKD1* mutations, develop SEGA earlier in childhood than do patients with a *TSC1* mutation and should be screened for SEGA from birth. Partial removal of SEGA is associated with a high risk of tumor regrowth, and these patients should be thoroughly followed by an experienced neurologist and have neuroimaging done more frequently. The risk factors for poor outcome of SEGA surgery identified in our study include: age <3 years, bilateral tumors, tumor size exceeding 2 cm, symptomatic SEGA, and partial SEGA surgery. In patients presenting any of these features, apart from acute hydrocephalus, pharmacotherapy with an mTOR inhibitor should be considered as a treatment option.

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*Courage is what it takes to stand up and speak; courage is also what it takes to sit down and listen.*

Winston Churchill