

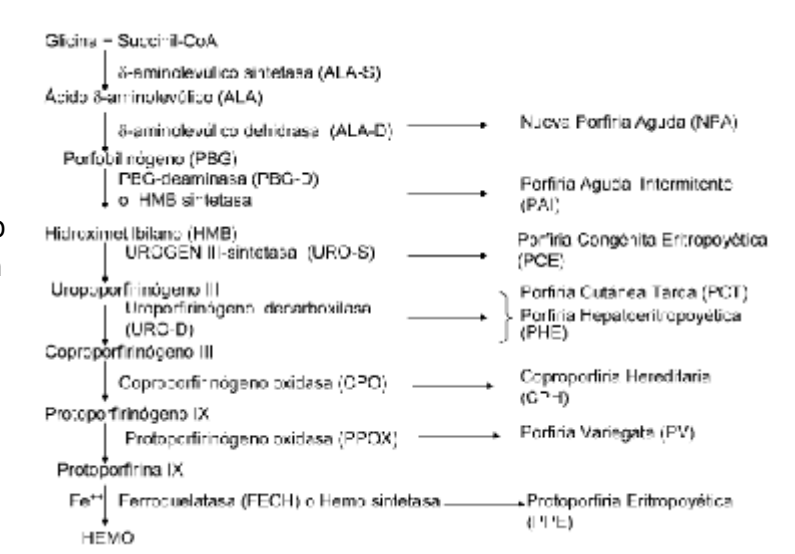
5-ALA

El ácido 5-aminolevulínico (5-ALA) es una pro-droga que causa **protoporfirinas** fluorescentes que se acumulan en los **gliomas** malignos.

La fluorescencia puede ser visualizada durante la cirugía por el uso de un microscopio modificado, que ayuda al cirujano a definir los márgenes del tumor. El tejido maligno provoca fluorescencia roja bajo iluminación con luz azul.

Con la ayuda de mapeo funcional hace que la resección sea viable en áreas elocuentes con tasas razonables de morbilidad tardía ¹⁾

Es un precursor de la síntesis del **grupo hemo**. Su administración exógena por vía oral puede inducir la acumulación de porfirinas fluorescentes (**protoporfirina IX**), en las células tumorales, de manera que cuando el tejido tumoral es iluminado con una luz violeta-azul (longitud de onda de entre 375 y 440 nm), se puede apreciar una fluorescencia roja resultado de la excitación de la protoporfirina IX acumulada. Esto permite la distinción intraoperatoria del tejido patológico, lo que facilita la resección tumoral y ayuda a conseguir mayores tasas de resección completa al detectar restos tumorales que, sin esta técnica, podrían pasar desapercibidos.



Se sugiere una asociación significativa, sin embargo, limitada, entre la ruptura de la **barrera hematoencefálica** y la porfirina inducida por el 5-ALA (Valdés y col., 2012).

Eficacia

La eficacia depende de la acumulación específica y la cantidad total de síntesis intracelular de protoporfirina IX (PpIX) en células tumorales

Stummer y col., publicaron sus resultados demostrando la utilidad del 5-ALA para mejorar el grado de la resección de gliomas cerebrales malignos (Stummer y col., 1998).

Añadido al mapeo intraoperatorio, conduce a una alta tasa de resecabilidad sin aumentar la tasa de morbilidad permanente (Schucht y col., 2012).

Desde entonces, la utilización de esta técnica está en franca difusión, habiéndose publicado artículos que hacen referencia a su utilidad en casos de lesiones distintas a los gliomas malignos.

Criterios de inclusión

Se pueden incluir todos los pacientes con sospecha de **glioma maligno** mediante TAC y/o Resonancia (Kamp y col., 2012).

En el estudio de Stummer y col., el 61% de los pacientes recibieron una resección total.

En ese estudio, los criterios de inclusión fueron

Tumor accesible a la resección completa (Stummer y col., 2006).

Histopatología confirmatoria de glioma maligno.

El uso no aprobado en pacientes pediátricos parece ser más útil en los gliomas recurrentes de alto grado. La acumulación de fluorescencia en otras entidades tumorales cerebrales pediátricos no es predecible y se debe evaluar en futuros estudios clínicos antes de ser integrado en los protocolos de tratamiento actuales ²⁾

[Cuestionario para pacientes pediátricos](#)

Administración

La dosis estándar preoperatoria es de 1.500 mg Gliolan (Medac, Alemania) disuelto en 50 ml de agua estéril 2-4 horas antes de la cirugía (un vial de Gliolan contiene 1.500 mg).

La dosis recomendada es de 20 mg / kg.

A los pacientes se les realiza una RM cerebral dentro de las primeras 72 horas postoperatorias, para determinar su estado de resección postoperatoria.

Evaluación postoperatoria

La evaluación de las imágenes postoperatorias se basan en secuencias T1 (FLAIR) sin y con contraste.

Si existe duda sobre el significado de un elemento se considera tumor residual.

Categorías de resección

Resección total

Resección subtotal (menos del 5% de tumor residual)

Tumor residual.

Seguridad

El estudio de Stummer y col., con posterior análisis del mismo conjunto de datos, demostró que las resecciones guiadas por fluorescencia son generalmente seguras (Stummer y col., 2006), pero tienen un riesgo ligeramente más alto de deterioro neurológico temporal - sobre todo en los pacientes con

déficit neurológico pre-existente, que no han respondido a los esteroides (Stummer y col., 2011).

Toxicidad

En la serie de Cortnum y Laursen, no hubo efectos secundarios tóxicos (Cortnum y Laursen, 2012).

Tumores intramedulares

El uso de la fluorescencia para la resección de tumores intramedulares ha sido comunicada previamente por otros autores. Arai et al. publicaron 3 casos de ependimomas intramedulares en los que la fluorescencia intraoperatoria del tejido tumoral fue de utilidad para conseguir la resección completa de las lesiones. Shimuzu et al. consiguen una resección completa de un ependimoma intramedular cervical gracias al uso de esta técnica (Bernal-García et al. 2010).

Método

Se ha creado un sistema de ablación por láser que puede proporcionar un análisis de alta precisión para la resección que con una mejora adicional, puede ser utilizado (Liao y col., 2012).

Gliomas malignos

El ácido 5-aminolevulínico (5-ALA) ha ganado importancia como un agente fotodinámico intraoperatorio de diagnóstico para la extirpación de los gliomas malignos.

Condujo a un aumento significativo en la incidencia de la resección completa (65% frente a 36%), la mejora de la supervivencia sin progresión en 6 meses (41% frente a 21%), y menos reintervenciones, así como el retraso en la aparición de deterioro neurológico (Colditz y col., 2012).

El significado de la fluorescencia de la pared ventricular durante el procedimiento, es aún desconocido.

La RM preoperatoria predice si existe apertura ventricular con la fluorescencia 5-ALA, según la localización tumoral, pero no predice, si la pared del ventrículo va a ser fluorescente o no. La fluorescencia de la pared del ventrículo no es un predictor de complicaciones o de supervivencia.

La localización del tumor periventricular es un factor independiente de mal pronóstico (Tejada-Solís y col., 2012).

Meningiomas

La aplicación de esta técnica para la resección de los meningiomas apenas ha sido explorado, en un total de 32 (97%) , la 5-ALA-fluorescencia inducida del tumor fue confirmado en un total de 31 (94%) pacientes. La fluorescencia no se correlacionaron con los hallazgos histológicos (n = 30 de OMS I-II, n = 1 de OMS grado III) o con edema cerebral preoperatorio y la administración de esteroides. No se observaron efectos adversos atribuibles a 5-ALA, concluyendo que es una herramienta intraoperatoria útil y prometedora para la visualización de meningioma (Coluccia 2010).

Permite una clara delimitación de tejido tumoral intraoperatorio de la duramadre adyacente, no afectada. A nivel microscópico, existe una correlación muy cerca de la fluorescencia de tumor, pero algunas células tumorales no presentan fluorescencia (Whitson et al. 2011).

Hemangioblastoma

Es un método útil para discernir si las células tumorales presentes en la pared del quiste peritumoral de un hemangioblastoma (Utsuki y col., 2011).

Ependimoma intramedular

Es útil para detectar los márgenes del tumor.

Cuando se combina con la monitorización electrofisiológica, puede ayudar a lograr la resección del tumor con seguridad máxima (Inoue y col., 2012).

Bibliografía

- Bernal-García, L.M., J.M. Cabezudo-Artero, M. Ortega-Martínez, I. Fernández-Portales, J. Giménez-Pando, L.F. Ugarriza-Echebarrieta, J. Mata-Gómez, M. Molina-Orozco, y J.F. Malca-Balcázar. 2010. Resección de tumor intramedular guiada por fluorescencia con ácido aminolevulínico. *Neurocirugía* 21, no. 4 (8). doi:10.4321/S1130-14732010000400004.
http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-14732010000400004&lng=en&nrm=iso&tlng=en.
- Colditz, Michael J, and Rosalind L Jeffree. 2012. "Aminolevulinic Acid (ALA)-protoporphyrin IX Fluorescence Guided Tumour Resection. Part 1: Clinical, Radiological and Pathological Studies." *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia* 19 (11) (November): 1471–1474. doi:10.1016/j.jocn.2012.03.009.
- Coluccia, Daniel, Javier Fandino, Masayuki Fujioka, Susanne Cordovi, Carl Muroi, y Hans Landolt. 2010. Intraoperative 5-aminolevulinic-acid-induced fluorescence in meningiomas. *Acta Neurochirurgica* (Junio 10). doi:10.1007/s00701-010-0708-4. <http://www.ncbi.nlm.nih.gov/pubmed/20535506>.
- Cortnum, Søren, and René Johannes Laursen. 2012. "Fluorescence-guided Resection of Gliomas." *Danish Medical Journal* 59 (8) (August): A4460.
- Inoue, Tomoo, Toshiki Endo, Kenichi Nagamatsu, Mika Watanabe, and Teiji Tominaga. 2012. "5-aminolevulinic Acid Fluorescence-guided Resection of Intramedullary Ependymoma: Report of 9 Cases." *Neurosurgery* (November 12). doi:10.1227/NEU.0b013e31827bc7a3.
- Kamp, Marcel A, Antonio Santacrose, Samis Zella, Dorothea C Reichelt, Jörg Felsberg, Hans-Jakob Steiger, Jan Frederick Cornelius, and Michael Sabel. 2012. "Is It a Glioblastoma? In Dubio Pro 5-ALA!" *Acta Neurochirurgica* 154 (7) (July): 1269–1273. doi:10.1007/s00701-012-1369-2.
- Liao, Hongen, Keisuke Fujiwara, Takehiro Ando, Takashi Maruyama, Etsuko Kobayashi, Yoshihiro Muragaki, Hiroshi Iseki, and Ichiro Sakuma. 2012. "Automatic Laser Scanning Ablation System for High-precision Treatment of Brain Tumors." *Lasers in Medical Science* (August 4). doi:10.1007/s10103-012-1164-6.
- Schucht, Philippe, Jürgen Beck, Janine Abu-Isa, Lukas Anderegg, Michael Murek, Kathleen Seidel, Lennard Stieglitz, and Andreas Raabe. 2012. "Gross Total Resection Rates in Contemporary Glioblastoma Surgery: Results of an Institutional Protocol Combining 5-ALA Intraoperative Fluorescence Imaging and Brain Mapping." *Neurosurgery* (August 14). doi:10.1227/NEU.0b013e31826d1e6b.

Stummer, W, S Stocker, S Wagner, H Stepp, C Fritsch, C Goetz, A E Goetz, R Kieffmann, and H J Reulen. 1998. "Intraoperative Detection of Malignant Gliomas by 5-aminolevulinic Acid-induced Porphyrin Fluorescence." *Neurosurgery* 42 (3) (March): 518-525; discussion 525-526.

Stummer W, Pichlmeier U, Meinel T et al. For the ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomized controlled multicentre phase III trial. *Lancet Oncol* 2006;7:392-401.

Stummer W, Tonn JG, Mehdorn HM et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. *J Neurosurg* 2011;114:613-23.

Tejada-Solís, Sonia, Guillermo Aldave-Orzaiz, Eva Pay-Valverde, Miguel Marigil-Sánchez, Miguel Angel Idoate-Gastearena, and Ricardo Díez-Valle. 2012. "Prognostic Value of Ventricular Wall Fluorescence During 5-aminolevulinic-guided Surgery for Glioblastoma." *Acta Neurochirurgica* (August 29). doi:10.1007/s00701-012-1475-1.

Utsuki, S. et al., 2011. Utility of intraoperative fluorescent diagnosis of residual hemangioblastoma using 5-aminolevulinic acid. *Neurology India*, 59(4), págs.612-615.

Valdés, Pablo A, Ziev B Moses, Anthony Kim, Clifford J Belden, Brian C Wilson, Keith D Paulsen, David W Roberts, and Brent T Harris. 2012. "Gadolinium- and 5-Aminolevulinic Acid-Induced Protoporphyrin IX Levels in Human Gliomas: An Ex Vivo Quantitative Study to Correlate Protoporphyrin IX Levels and Blood-Brain Barrier Breakdown." *Journal of Neuropathology and Experimental Neurology* 71 (9) (September): 806-813. doi:10.1097/NEN.0b013e31826775a1.

Whitson, Wesley J, Pablo A Valdes, Brent T Harris, Keith D Paulsen, y David W Roberts. 2011. Confocal Microscopy for the Histologic Fluorescence Pattern of a Recurrent Atypical Meningioma. *Neurosurgery* (Marzo 8). doi:10.1227/NEU.0b013e318217163c. <http://www.ncbi.nlm.nih.gov/pubmed/21389893>.

Bibliografía recomendada

1: Utsuki S, Oka H, Kijima C, Miyajima Y, Hagiwara H, Fujii K. Utility of intraoperative fluorescent diagnosis of residual hemangioblastoma using 5-aminolevulinic acid. *Neurol India*. 2011 Jul-Aug;59(4):612-5. PubMed PMID: 21891945.

2: Ohmura T, Fukushima T, Shibaguchi H, Yoshizawa S, Inoue T, Kuroki M, Sasaki K, Umemura S. Sonodynamic therapy with 5-aminolevulinic acid and focused ultrasound for deep-seated intracranial glioma in rat. *Anticancer Res*. 2011 Jul;31(7):2527-33. PubMed PMID: 21873170.

3: Etminan N, Peters C, Lakbir D, Bünemann E, Börger V, Sabel MC, Hänggi D, Steiger HJ, Stummer W, Sorg RV. Heat-shock protein 70-dependent dendritic cell activation by 5-aminolevulinic acid-mediated photodynamic treatment of human glioblastoma spheroids in vitro. *Br J Cancer*. 2011 Sep 27;105(7):961-9. doi: 10.1038/bjc.2011.327. Epub 2011 Aug 23. PubMed PMID: 21863026.

4: Tsugu A, Ishizaka H, Mizokami Y, Osada T, Baba T, Yoshiyama M, Nishiyama J, Matsumae M. Impact of the combination of 5-aminolevulinic acid-induced fluorescence with intraoperative magnetic resonance imaging-guided surgery for glioma. *World Neurosurg*. 2011 Jul-Aug;76(1-2):120-7. PubMed PMID: 21839963.

5: Arita H, Kinoshita M, Kagawa N, Fujimoto Y, Kishima H, Hashimoto N, Yoshimine T. (11) C-

methionine uptake and intraoperative 5-aminolevulinic acid-induced fluorescence as separate index markers of cell density in glioma: A stereotactic image-histological analysis. *Cancer*. 2011 Aug 11. doi: 10.1002/cncr.26445. [Epub ahead of print] PubMed PMID: 21837671.

6: Takahashi K, Ikeda N, Nonoguchi N, Kajimoto Y, Miyatake SI, Hagiya Y, Ogura SI, Nakagawa H, Ishikawa T, Kuroiwa T. Enhanced expression of coproporphyrinogen oxidase in malignant brain tumors: CPOX expression and 5-ALA-induced fluorescence. *Neuro Oncol*. 2011 Aug 8. [Epub ahead of print] PubMed PMID: 21824890.

7: Kamoshima Y, Terasaka S, Kuroda S, Iwasaki Y. Morphological and histological changes of glioma cells immediately after 5-aminolevulinic acid mediated photodynamic therapy. *Neurol Res*. 2011 Sep;33(7):739-46. PubMed PMID: 21756554.

8: Moriuchi S, Yamada K, Dehara M, Teramoto Y, Soda T, Imakita M, Taneda M. Use of 5-aminolevulinic acid for the confirmation of deep-seated brain tumors during stereotactic biopsy. Report of 2 cases. *J Neurosurg*. 2011 Aug;115(2):278-80. Epub 2011 May 6. PubMed PMID: 21548751.

9: Bekelis K, Valdés PA, Erkmen K, Leblond F, Kim A, Wilson BC, Harris BT, Paulsen KD, Roberts DW. Quantitative and qualitative 5-aminolevulinic acid-induced protoporphyrin IX fluorescence in skull base meningiomas. *Neurosurg Focus*. 2011 May;30(5):E8. PubMed PMID: 21529179; PubMed Central PMCID: PMC3116440.

10: Etminan N, Peters C, Ficnar J, Anlasik S, Bünemann E, Slotty PJ, Hänggi D, Steiger HJ, Sorg RV, Stummer W. Modulation of migratory activity and invasiveness of human glioma spheroids following 5-aminolevulinic acid-based photodynamic treatment. Laboratory investigation. *J Neurosurg*. 2011 Aug;115(2):281-8. Epub 2011 Apr 22. PubMed PMID: 21513432.

11: Whitson WJ, Valdes PA, Harris BT, Paulsen KD, Roberts DW. Confocal microscopy for the histological fluorescence pattern of a recurrent atypical meningioma: case report. *Neurosurgery*. 2011 Jun;68(6):E1768-72; discussion E1772-3. PubMed PMID: 21389893.

12: Sherman JH, Hoes K, Marcus J, Komotar RJ, Brennan CW, Gutin PH. Neurosurgery for brain tumors: update on recent technical advances. *Curr Neurol Neurosci Rep*. 2011 Jun;11(3):313-9. Review. PubMed PMID: 21327735.

13: Kostron H, Bauer R. Management of recurrent malignant glioma-neurosurgical strategies. *Wien Med Wochenschr*. 2011 Jan;161(1-2):20-1. Review. PubMed PMID: 21312095.

14: Teng L, Nakada M, Zhao SG, Endo Y, Furuyama N, Nambu E, Pyko IV, Hayashi Y, Hamada JI. Silencing of ferrochelatase enhances 5-aminolevulinic acid-based fluorescence and photodynamic therapy efficacy. *Br J Cancer*. 2011 Mar 1;104(5):798-807. Epub 2011 Feb 8. PubMed PMID: 21304523; PubMed Central PMCID: PMC3048207.

15: Park CK. Hemangioblastoma. *J Neurosurg*. 2011 Mar;114(3):886; author reply 886-7. Epub 2011 Jan 28. PubMed PMID: 21275559.

16: Tanaka S, Nakada M, Hayashi Y, Nakada S, Sawada-Kitamura S, Furuyama N, Suzuki T, Kamide T, Hayashi Y, Yano S, Hamada J. Epithelioid glioblastoma changed to typical glioblastoma: the methylation status of MGMT promoter and 5-ALA fluorescence. *Brain Tumor Pathol*. 2011 Feb;28(1):59-64. Epub 2010 Dec 25. PubMed PMID: 21188541.

17: Liao H, Noguchi M, Maruyama T, Muragaki Y, Kobayashi E, Iseki H, Sakuma I. An integrated diagnosis and therapeutic system using intra-operative 5-aminolevulinic-acid-induced fluorescence

guided robotic laser ablation for precision neurosurgery. *Med Image Anal.* 2010 Nov 28. [Epub ahead of print] PubMed PMID: 21183395.

18: Ritz R, Feigl GC, Schuhmann MU, Ehrhardt A, Danz S, Noell S, Bornemann A, Tatagiba MS. Use of 5-ALA fluorescence guided endoscopic biopsy of a deep-seated primary malignant brain tumor. *J Neurosurg.* 2011 May;114(5):1410-3. Epub 2010 Dec 17. PubMed PMID: 21166571.

19: Floeth FW, Sabel M, Ewelt C, Stummer W, Felsberg J, Reifenberger G, Steiger HJ, Stoffels G, Coenen HH, Langen KJ. Comparison of (18)F-FET PET and 5-ALA fluorescence in cerebral gliomas. *Eur J Nucl Med Mol Imaging.* 2011 Apr;38(4):731-41. Epub 2010 Dec 10. PubMed PMID: 21153408.

20: Roessler K, Zachenhofer I. Anaplastic foci within gliomas. *Neurosurgery.* 2011 Feb;68(2):E592; author reply E593. PubMed PMID: 21150485.

21: Hefti M, Holenstein F, Albert I, Looser H, Luginbuehl V. Susceptibility to 5-aminolevulinic acid based photodynamic therapy in WHO I meningioma cells corresponds to ferrochelatase activity. *Photochem Photobiol.* 2011 Jan-Feb;87(1):235-41. doi: 10.1111/j.1751-1097.2010.00821.x. Epub 2010 Nov 12. PubMed PMID: 21073472.

22: Muragaki Y, Iseki H, Maruyama T, Tanaka M, Shinohara C, Suzuki T, Yoshimitsu K, Ikuta S, Hayashi M, Chernov M, Hori T, Okada Y, Takakura K. Information-guided surgical management of gliomas using low-field-strength intraoperative MRI. *Acta Neurochir Suppl.* 2011;109:67-72. PubMed PMID: 20960323.

23: Eicker S, Sarikaya-Seiwert S, Borkhardt A, Gierga K, Turowski B, Heiroth HJ, Steiger HJ, Stummer W. ALA-induced porphyrin accumulation in medulloblastoma and its use for fluorescence-guided surgery. *Cen Eur Neurosurg.* 2011 May;72(2):101-3. Epub 2010 Oct 7. PubMed PMID: 20931449.

24: Stummer W, Nestler U, Stockhammer F, Krex D, Kern BC, Mehdorn HM, Vince GH, Pichlmeier U. Favorable outcome in the elderly cohort treated by concomitant temozolomide radiochemotherapy in a multicentric phase II safety study of 5-ALA. *J Neurooncol.* 2011 Jun;103(2):361-70. Epub 2010 Oct 5. PubMed PMID: 20922459.

25: Bernal-García LM, Cabezudo-Artero JM, Ortega-Martínez M, Fernández-Portales I, Giménez-Pando J, Ugarriza-Echebarrieta LF, Mata-Gómez J, Molina-Orozco M, Malca-Balcázar JF. [Fluorescence-guided resection with 5-aminolevulinic acid of an intramedullary tumor]. *Neurocirugia (Astur).* 2010 Aug;21(4):312-6. Spanish. PubMed PMID: 20725700.

26: Pogue BW, Gibbs-Strauss S, Valdés PA, Samkoe K, Roberts DW, Paulsen KD. Review of Neurosurgical Fluorescence Imaging Methodologies. *IEEE J Sel Top Quantum Electron.* 2010 May;16(3):493-505. PubMed PMID: 20671936; PubMed Central PMCID: PMC2910912.

27: Fernández-Candil J, Pacreu S, Villaba G, Fernández GS. [Anesthetic approach and implications of the use of 5-aminolevulinic acid as a tumor marker in the resection of malignant gliomas]. *Rev Esp Anesthesiol Reanim.* 2010 Jun-Jul;57(6):395-6. Spanish. PubMed PMID: 20645499.

28: Carretero M, Negrete N, Muñoz G, Sánchez J, Bernal LM. [Anesthetic treatment during resection of high-grade malignant gliomas after injection of 5-aminolevulinic acid to enhance intraoperative visualization]. *Rev Esp Anesthesiol Reanim.* 2010 Jun-Jul;57(6):393-5. Spanish. PubMed PMID: 20645498.

29: Engh JA. Improving intraoperative visualization of anaplastic foci within gliomas. *Neurosurgery.* 2010 Aug;67(2):N21-2. PubMed PMID: 20644407.

- 30: Díez Valle R, Tejada Solis S, Idoate Gastearena MA, García de Eulate R, Domínguez Echávarri P, Aristu Mendiroz J. Surgery guided by 5-aminolevulinic fluorescence in glioblastoma: volumetric analysis of extent of resection in single-center experience. *J Neurooncol*. 2011 Mar;102(1):105-13. Epub 2010 Jul 6. PubMed PMID: 20607351.
- 31: Coluccia D, Fandino J, Fujioka M, Cordovi S, Muroi C, Landolt H. Intraoperative 5-aminolevulinic-acid-induced fluorescence in meningiomas. *Acta Neurochir (Wien)*. 2010 Oct;152(10):1711-9. Epub 2010 Jun 10. PubMed PMID: 20535506.
- 32: Stummer W, Tonn JC, Mehdorn HM, Nestler U, Franz K, Goetz C, Bink A, Pichlmeier U; ALA-Glioma Study Group. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. *Clinical article. J Neurosurg*. 2011 Mar;114(3):613-23. Epub 2010 Apr 16. PubMed PMID: 20397896.
- 33: Roberts DW, Valdés PA, Harris BT, Fontaine KM, Hartov A, Fan X, Ji S, Lollis SS, Pogue BW, Leblond F, Tosteson TD, Wilson BC, Paulsen KD. Coregistered fluorescence-enhanced tumor resection of malignant glioma: relationships between δ -aminolevulinic acid-induced protoporphyrin IX fluorescence, magnetic resonance imaging enhancement, and neuropathological parameters. *Clinical article. J Neurosurg*. 2011 Mar;114(3):595-603. Epub 2010 Apr 9. PubMed PMID: 20380535; PubMed Central PMCID: PMC2921008.
- 34: Widhalm G, Wolfsberger S, Minchev G, Woehrer A, Krssak M, Czech T, Prayer D, Asenbaum S, Hainfellner JA, Knosp E. 5-Aminolevulinic acid is a promising marker for detection of anaplastic foci in diffusely infiltrating gliomas with nonsignificant contrast enhancement. *Cancer*. 2010 Mar 15;116(6):1545-52. PubMed PMID: 20108311.
- 35: Ewelt C, Stummer W, Klink B, Felsberg J, Steiger HJ, Sabel M. Corpectomy as final treatment option for diffuse intramedullary malignant glioma using 5-ALA fluorescence-guided resection. *Clin Neurol Neurosurg*. 2010 May;112(4):357-61. Epub 2010 Jan 12. PubMed PMID: 20061079.
- 36: Nabavi A, Thurm H, Zountsas B, Pietsch T, Lanfermann H, Pichlmeier U, Mehdorn M; 5-ALA Recurrent Glioma Study Group. Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: a phase ii study. *Neurosurgery*. 2009 Dec;65(6):1070-6; discussion 1076-7. PubMed PMID: 19934966.
- 37: Feigl GC, Ritz R, Moraes M, Klein J, Ramina K, Gharabaghi A, Krischek B, Danz S, Bornemann A, Liebsch M, Tatagiba MS. Resection of malignant brain tumors in eloquent cortical areas: a new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring. *J Neurosurg*. 2010 Aug;113(2):352-7. PubMed PMID: 19911888.
- 38: Ruge JR, Liu J. Use of 5-aminolevulinic acid for visualization and resection of a benign pediatric brain tumor. *J Neurosurg Pediatr*. 2009 Nov;4(5):484-6. PubMed PMID: 19877785.
- 39: Hayashi Y, Nakada M, Tanaka S, Uchiyama N, Hayashi Y, Kita D, Hamada J. Implication of 5-aminolevulinic acid fluorescence of the ventricular wall for postoperative communicating hydrocephalus associated with cerebrospinal fluid dissemination in patients with glioblastoma multiforme: a report of 7 cases. *J Neurosurg*. 2010 May;112(5):1015-9. PubMed PMID: 19747042.
- 40: Stummer W, Kamp MA. The importance of surgical resection in malignant glioma. *Curr Opin Neurol*. 2009 Dec;22(6):645-9. Review. PubMed PMID: 19738467.
- 41: Stockhammer F, Misch M, Horn P, Koch A, Fonyuy N, Plotkin M. Association of F18-fluoro-ethyl-tyrosin uptake and 5-aminolevulinic acid-induced fluorescence in gliomas. *Acta Neurochir (Wien)*.

2009 Nov;151(11):1377-83. Epub 2009 Jul 29. PubMed PMID: 19639250.

42: Miyatake S, Kajimoto Y, Kuroiwa T. [Intraoperative photo-dynamic diagnosis of brain tumors]. Brain Nerve. 2009 Jul;61(7):835-42. Review. Japanese. PubMed PMID: 19618861.

43: Xiao H, Liao Q, Cheng M, Li F, Xie B, Li M, Feng H. 5-Amino-4-oxopentanoic acid photodynamic diagnosis guided microsurgery and photodynamic therapy on VX2 brain tumour implanted in a rabbit model. Chin Med J (Engl). 2009 Jun 5;122(11):1316-21. PubMed PMID: 19567144.

44: Utsuki S, Oka H, Sato K, Shimizu S, Suzuki S, Fujii K. Fluorescence diagnosis of tumor cells in hemangioblastoma cysts with 5-aminolevulinic acid. J Neurosurg. 2010 Jan;112(1):130-2. PubMed PMID: 19480541.

45: Tsurubuchi T, Zoboronok A, Yamamoto T, Nakai K, Yoshida F, Shirakawa M, Matsuda M, Matsumura A. The optimization of fluorescence imaging of brain tumor tissue differentiated from brain edema-in vivo kinetic study of 5-aminolevulinic acid and talaporfin sodium. Photodiagnosis Photodyn Ther. 2009 Mar;6(1):19-27. Epub 2009 May 5. PubMed PMID: 19447368.

46: Eljamel MS, Leese G, Moseley H. Intraoperative optical identification of pituitary adenomas. J Neurooncol. 2009 May;92(3):417-21. Epub 2009 Apr 9. PubMed PMID: 19357967.

47: Eljamel MS. Which intracranial lesions would be suitable for 5-aminolevulinic acid-induced fluorescence-guided identification, localization, or resection? A prospective study of 114 consecutive intracranial lesions. Clin Neurosurg. 2009;56:93-7. PubMed PMID: 20214039.

48: Liao H, Shimaya K, Wang K, Maruyama T, Noguchi M, Muragaki Y, Kobayashi E, Iseki H, Sakuma I. Combination of intraoperative 5-aminolevulinic acid-induced fluorescence and 3-D MR imaging for guidance of robotic laser ablation for precision neurosurgery. Med Image Comput Comput Assist Interv. 2008;11(Pt 2):373-80. PubMed PMID: 18982627.

49: Toda M. Intraoperative navigation and fluorescence imagings in malignant glioma surgery. Keio J Med. 2008 Sep;57(3):155-61. PubMed PMID: 18854668.

50: Pichlmeier U, Bink A, Schackert G, Stummer W; ALA Glioma Study Group. Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. Neuro Oncol. 2008 Dec;10(6):1025-34. Epub 2008 Jul 30. PubMed PMID: 18667747; PubMed Central PMCID: PMC2719000.

51: Kamoshima Y, Terasaka S, Iwasaki Y. [Photodynamic therapy mediated with 5-aminolevulinic acid for C6 glioma spheroids]. Hokkaido Igaku Zasshi. 2008 May;83(3):167-73. Japanese. PubMed PMID: 18546870.

52: Morofuji Y, Matsuo T, Hayashi Y, Suyama K, Nagata I. Usefulness of intraoperative photodynamic diagnosis using 5-aminolevulinic acid for meningiomas with cranial invasion: technical case report. Neurosurgery. 2008 Mar;62(3 Suppl 1):102-3; discussion 103-4. PubMed PMID: 18424972.

53: Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T; ALA-Glioma Study Group. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery. 2008 Mar;62(3):564-76; discussion 564-76. PubMed PMID: 18425006.

54: Kantelhardt SR, Diddens H, Leppert J, Rohde V, Hüttmann G, Giese A. Multiphoton excitation fluorescence microscopy of 5-aminolevulinic acid induced fluorescence in experimental gliomas.

Lasers Surg Med. 2008 Apr;40(4):273-81. PubMed PMID: 18412229.

55: Krammer B, Plaetzer K. ALA and its clinical impact, from bench to bedside. Photochem Photobiol Sci. 2008 Mar;7(3):283-9. Epub 2007 Dec 7. Review. PubMed PMID: 18389144.

56: Hefti M, von Campe G, Moschopoulos M, Siegner A, Looser H, Landolt H. 5-aminolevulinic acid induced protoporphyrin IX fluorescence in high-grade glioma surgery: a one-year experience at a single institution. Swiss Med Wkly. 2008 Mar 22;138(11-12):180-5. PubMed PMID: 18363116.

57: Luckers O, James S, Ghassempour K, Maertens de Noordhout A, Born JD. [Image of the month. 5-aminolevulinic acid (5-ALA) in the guided treatment of malignant brain tumors]. Rev Med Liege. 2008 Jan;63(1):4-5. French. PubMed PMID: 18303677.

58: Utsuki S, Oka H, Miyajima Y, Shimizu S, Suzuki S, Fujii K. Auditory alert system for fluorescence-guided resection of gliomas. Neurol Med Chir (Tokyo). 2008 Feb;48(2):95-7; discussion 97-8. PubMed PMID: 18296881.

59: Koc K, Anik I, Cabuk B, Ceylan S. Fluorescein sodium-guided surgery in glioblastoma multiforme: a prospective evaluation. Br J Neurosurg. 2008 Feb;22(1):99-103. PubMed PMID: 18224529.

60: Okuda T, Kataoka K, Taneda M. Metastatic brain tumor surgery using fluorescein sodium: technical note. Minim Invasive Neurosurg. 2007 Dec;50(6):382-4. PubMed PMID: 18210365.

61: Tonn JC, Stummer W. Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: practical use, risks, and pitfalls. Clin Neurosurg. 2008;55:20-6. Review. PubMed PMID: 19248665.

62: Utsuki S, Miyoshi N, Oka H, Miyajima Y, Shimizu S, Suzuki S, Fujii K. Fluorescence-guided resection of metastatic brain tumors using a 5-aminolevulinic acid-induced protoporphyrin IX: pathological study. Brain Tumor Pathol. 2007;24(2):53-5. Epub 2007 Nov 28. PubMed PMID: 18095131.

63: Miyatake S, Kuroiwa T, Kajimoto Y, Miyashita M, Tanaka H, Tsuji M. Fluorescence of non-neoplastic, magnetic resonance imaging-enhancing tissue by 5-aminolevulinic acid: case report. Neurosurgery. 2007 Nov;61(5):E1101-3; discussion E1103-4. PubMed PMID: 18091261.

64: Stummer W, Beck T, Beyer W, Mehrkens JH, Obermeier A, Etminan N, Stepp H, Tonn JC, Baumgartner R, Herms J, Kreth FW. Long-sustaining response in a patient with non-resectable, distant recurrence of glioblastoma multiforme treated by interstitial photodynamic therapy using 5-ALA: case report. J Neurooncol. 2008 Mar;87(1):103-9. Epub 2007 Nov 23. PubMed PMID: 18034212.

65: Morofuji Y, Matsuo T, Toyoda K, Takeshita T, Hirose M, Hirao T, Hayashi Y, Tsutsumi K, Abe K, Nagata I. [Skull metastasis of hepatocellular carcinoma successfully treated by intraoperative photodynamic diagnosis using 5-aminolevulinic acid: case report]. No Shinkei Geka. 2007 Sep;35(9):913-8. Japanese. PubMed PMID: 17867312.

66: Stepp H, Beck T, Pongratz T, Meinel T, Kreth FW, Tonn JC, Stummer W. ALA and malignant glioma: fluorescence-guided resection and photodynamic treatment. J Environ Pathol Toxicol Oncol. 2007;26(2):157-64. PubMed PMID: 17725542.

67: Beck TJ, Kreth FW, Beyer W, Mehrkens JH, Obermeier A, Stepp H, Stummer W, Baumgartner R. Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX. Lasers Surg Med. 2007 Jun;39(5):386-93. PubMed PMID: 17565715.

- 68: Kajimoto Y, Kuroiwa T, Miyatake S, Ichioka T, Miyashita M, Tanaka H, Tsuji M. Use of 5-aminolevulinic acid in fluorescence-guided resection of meningioma with high risk of recurrence. Case report. *J Neurosurg*. 2007 Jun;106(6):1070-4. PubMed PMID: 17564181.
- 69: Utsuki S, Oka H, Sato S, Shimizu S, Suzuki S, Tanizaki Y, Kondo K, Miyajima Y, Fujii K. Histological examination of false positive tissue resection using 5-aminolevulinic acid-induced fluorescence guidance. *Neurol Med Chir (Tokyo)*. 2007 May;47(5):210-3; discussion 213-4. PubMed PMID: 17527047.
- 70: Tamura Y, Kuroiwa T, Kajimoto Y, Miki Y, Miyatake S, Tsuji M. Endoscopic identification and biopsy sampling of an intraventricular malignant glioma using a 5-aminolevulinic acid-induced protoporphyrin IX fluorescence imaging system. Technical note. *J Neurosurg*. 2007 Mar;106(3):507-10. PubMed PMID: 17367078.
- 71: Inoue H, Kajimoto Y, Shibata MA, Miyoshi N, Ogawa N, Miyatake S, Otsuki Y, Kuroiwa T. Massive apoptotic cell death of human glioma cells via a mitochondrial pathway following 5-aminolevulinic acid-mediated photodynamic therapy. *J Neurooncol*. 2007 Jul;83(3):223-31. Epub 2007 Jan 24. PubMed PMID: 17245620.
- 72: Löning M, Diddens H, Friedrich M, Altgassen C, Diedrich K, Hüttmann G. [Fluorescence diagnosis and photodynamic therapy with 5-aminolevulinic acid induced protoporphyrin IX in gynecology: an overview]. *Zentralbl Gynakol*. 2006 Dec;128(6):311-7. Review. German. PubMed PMID: 17213968.
- 73: Yamaguchi F, Teramoto A, Takahashi H. [5-ALA fluorescence guided tumor resection]. *No To Shinkei*. 2006 Dec;58(12):1027-33. Japanese. PubMed PMID: 17193952.
- 74: Yamamoto J, Yamamoto S, Hirano T, Li S, Koide M, Kohno E, Okada M, Inenaga C, Tokuyama T, Yokota N, Terakawa S, Namba H. Monitoring of singlet oxygen is useful for predicting the photodynamic effects in the treatment for experimental glioma. *Clin Cancer Res*. 2006 Dec 1;12(23):7132-9. PubMed PMID: 17145838.
- 75: Shimizu S, Utsuki S, Sato K, Oka H, Fujii K, Mii K. Photodynamic diagnosis in surgery for spinal ependymoma. Case illustration. *J Neurosurg Spine*. 2006 Oct;5(4):380. PubMed PMID: 17048778.
- 76: Xiang J, Hu Y, Smith DE, Keep RF. PEPT2-mediated transport of 5-aminolevulinic acid and carnosine in astrocytes. *Brain Res*. 2006 Nov 29;1122(1):18-23. Epub 2006 Oct 10. PubMed PMID: 17034769; PubMed Central PMCID: PMC1829310.
- 77: Zelenkov P, Baumgartner R, Bise K, Heide M, Meier R, Stocker S, Sroka R, Goldbrunner R, Stummer W. Acute morphological sequelae of photodynamic therapy with 5-aminolevulinic acid in the C6 spheroid model. *J Neurooncol*. 2007 Mar;82(1):49-60. Epub 2006 Sep 27. PubMed PMID: 17004102.
- 78: Hirschberg H, Spetälen S, Carper S, Hole P, Tillung T, Madsen S. Minimally invasive photodynamic therapy (PDT) for ablation of experimental rat glioma. *Minim Invasive Neurosurg*. 2006 Jun;49(3):135-42. PubMed PMID: 16921452.
- 79: Arai T, Tani S, Isoshima A, Nagashima H, Joki T, Takahashi-Fujigasaki J, Abe T. [Intraoperative photodynamic diagnosis for spinal ependymoma using 5-aminolevulinic acid: technical note]. *No Shinkei Geka*. 2006 Aug;34(8):811-7. Japanese. PubMed PMID: 16910494.
- 80: Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol*. 2006 May;7(5):392-401. PubMed

PMID: 16648043.

- 81: Utsuki S, Oka H, Sato S, Suzuki S, Shimizu S, Tanaka S, Fujii K. Possibility of using laser spectroscopy for the intraoperative detection of nonfluorescing brain tumors and the boundaries of brain tumor infiltrates. Technical note. *J Neurosurg*. 2006 Apr;104(4):618-20. PubMed PMID: 16619668.
- 82: Hirschberg H, Sørensen DR, Angell-Petersen E, Peng Q, Tromberg B, Sun CH, Spetälen S, Madsen S. Repetitive photodynamic therapy of malignant brain tumors. *J Environ Pathol Toxicol Oncol*. 2006;25(1-2):261-79. Review. PubMed PMID: 16566723.
- 83: Maruyama T. [Intraoperative photodynamic diagnosis using 5-ALA for glioma surgery]. *Nihon Rinsho*. 2005 Sep;63 Suppl 9:380-8. Review. Japanese. PubMed PMID: 16201551.
- 84: Tsai JC, Wu CL, Chien HF, Chen CT. Reorganization of cytoskeleton induced by 5-aminolevulinic acid-mediated photodynamic therapy and its correlation with mitochondrial dysfunction. *Lasers Surg Med*. 2005 Jun;36(5):398-408. PubMed PMID: 15856508.
- 85: Sonoda Y, Kamaya T. [New development of surgical treatment for malignant brain tumors]. *Gan To Kagaku Ryoho*. 2005 Apr;32(4):437-41. Japanese. PubMed PMID: 15853206.
- 86: Duffner F, Ritz R, Freudenstein D, Weller M, Dietz K, Wessels J. Specific intensity imaging for glioblastoma and neural cell cultures with 5-aminolevulinic acid-derived protoporphyrin IX. *J Neurooncol*. 2005 Jan;71(2):107-11. PubMed PMID: 15690124.
- 87: Hirschberg H, Sun CH, Tromberg BJ, Yeh AT, Madsen SJ. Enhanced cytotoxic effects of 5-aminolevulinic acid-mediated photodynamic therapy by concurrent hyperthermia in glioma spheroids. *J Neurooncol*. 2004 Dec;70(3):289-99. PubMed PMID: 15662970.
- 88: Ito S, Rachinger W, Stepp H, Reulen HJ, Stummer W. Oedema formation in experimental photo-irradiation therapy of brain tumours using 5-ALA. *Acta Neurochir (Wien)*. 2005 Jan;147(1):57-65; discussion 65. PubMed PMID: 15565479.
- 89: Bogaards A, Varma A, Collens SP, Lin A, Giles A, Yang VX, Bilbao JM, Lilge LD, Muller PJ, Wilson BC. Increased brain tumor resection using fluorescence image guidance in a preclinical model. *Lasers Surg Med*. 2004;35(3):181-90. PubMed PMID: 15389738.
- 90: Grieb P. [5-Aminolevulinic acid (ALA) and its applications in neurosurgery]. *Neurol Neurochir Pol*. 2004 May-Jun;38(3):201-7. Review. Polish. PubMed PMID: 15354233.
- 91: Tsai JC, Chiang CP, Chen HM, Huang SB, Wang CW, Lee MI, Hsu YC, Chen CT, Tsai T. Photodynamic Therapy of oral dysplasia with topical 5-aminolevulinic acid and light-emitting diode array. *Lasers Surg Med*. 2004;34(1):18-24. PubMed PMID: 14755421.
- 92: Stummer W, Reulen HJ, Novotny A, Stepp H, Tonn JC. Fluorescence-guided resections of malignant gliomas—an overview. *Acta Neurochir Suppl*. 2003;88:9-12. PubMed PMID: 14531555.
- 93: Eljamel MS. New light on the brain: The role of photosensitizing agents and laser light in the management of invasive intracranial tumors. *Technol Cancer Res Treat*. 2003 Aug;2(4):303-9. Review. PubMed PMID: 12892512.
- 94: Ennis SR, Novotny A, Xiang J, Shakui P, Masada T, Stummer W, Smith DE, Keep RF. Transport of 5-aminolevulinic acid between blood and brain. *Brain Res*. 2003 Jan 10;959(2):226-34. PubMed PMID:

12493610.

95: Dalbasti T, Cagli S, Kilinc E, Oktar N, Ozsoz M. Online electrochemical monitoring of nitric oxide during photodynamic therapy. *Nitric Oxide*. 2002 Dec;7(4):301-5. PubMed PMID: 12446180.

96: Olzowy B, Hundt CS, Stocker S, Bise K, Reulen HJ, Stummer W. Photoirradiation therapy of experimental malignant glioma with 5-aminolevulinic acid. *J Neurosurg*. 2002 Oct;97(4):970-6. PubMed PMID: 12405389.

97: Hirschberg H, Sun CH, Tromberg BJ, Madsen SJ. ALA- and ALA-ester-mediated photodynamic therapy of human glioma spheroids. *J Neurooncol*. 2002 Mar;57(1):1-7. PubMed PMID: 12125962.

98: Kaneko S. [Intraoperative photodynamic diagnosis of human glioma using ALA induced protoporphyrin IX]. *No Shinkei Geka*. 2001 Nov;29(11):1019-31. Review. Japanese. PubMed PMID: 11758309.

99: Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. *J Neurosurg*. 2000 Dec;93(6):1003-13. PubMed PMID: 11117842.

100: Novotny A, Xiang J, Stummer W, Teuscher NS, Smith DE, Keep RF. Mechanisms of 5-aminolevulinic acid uptake at the choroid plexus. *J Neurochem*. 2000 Jul;75(1):321-8. PubMed PMID: 10854277.

101: Stummer W, Stocker S, Novotny A, Heimann A, Sauer O, Kempfski O, Plesnila N, Wietzorrek J, Reulen HJ. In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. *J Photochem Photobiol B*. 1998 Sep;45(2-3):160-9. PubMed PMID: 9868806.

102: Stummer W, Stepp H, Möller G, Ehrhardt A, Leonhard M, Reulen HJ. Technical principles for protoporphyrin-IX-fluorescence guided microsurgical resection of malignant glioma tissue. *Acta Neurochir (Wien)*. 1998;140(10):995-1000. PubMed PMID: 9856241.

103: Obwegeser A, Jakober R, Kostron H. Uptake and kinetics of ¹⁴C-labelled meta-tetrahydroxyphenylchlorin and 5-aminolaevulinic acid in the C6 rat glioma model. *Br J Cancer*. 1998 Sep;78(6):733-8. PubMed PMID: 9743291; PubMed Central PMCID: PMC2062980.

104: Stummer W, Stocker S, Wagner S, Stepp H, Fritsch C, Goetz C, Goetz AE, Kieffmann R, Reulen HJ. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. *Neurosurgery*. 1998 Mar;42(3):518-25; discussion 525-6. PubMed PMID: 9526986.

1)

Della Puppa A, De Pellegrin S, d'Avella E, Gioffrè G, Rossetto M, Gerardi A, Lombardi G, Manara R, Munari M, Saladini M, Scienza R. 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature. *Acta Neurochir (Wien)*. 2013 Jun;155(6):965-72; discussion 972. doi: 10.1007/s00701-013-1660-x. Epub 2013 Mar 7. PubMed PMID: 23468036.

2)

Preuß M, Renner C, Krupp W, Christiansen H, Fischer L, Merckenschlager A, Kieß W, Müller W, Manzo N, Meixensberger J, Nestler U. The use of 5-aminolevulinic acid fluorescence guidance in resection of pediatric brain tumors. *Childs Nerv Syst*. 2013 Aug;29(8):1263-7. doi: 10.1007/s00381-013-2159-8. Epub 2013 May 25. PubMed PMID: 23708867.

From:

<http://www.neurocirugiacontemporanea.com/> - **Neurocirugía Contemporánea**
ISSN 1988-2661

Permanent link:

<http://www.neurocirugiacontemporanea.com/doku.php?id=5-ala>

Last update: **2019/09/26 22:18**

