Intraoperative cell-cycle analysis to guide brain tumor removal

We read with great interest the recent article by Santagata et al. (1) on the value of intraoperative mass spectrometry during brain tumor surgery. The authors, using desorption electrospray ionization (DESI) MS, detected rapidly the tumor metabolite 2-hydroxyglutarate (2-HG) from tissue sections of surgically resected gliomas. With DESI MS the authors identified isocitrate dehydrogenase 1-mutant tumors with both high sensitivity and specificity, providing diagnostic, prognostic, and predictive information. Furthermore, 2-HG levels correlated with tumor content, thereby indicating tumor margins (1).

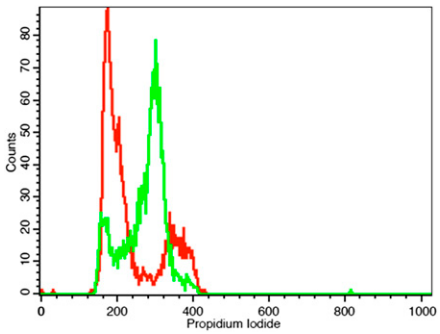

Fig. 1. A glioblastoma case and the overlay of the two histograms, from tumor core (green) and perilesional tissue (red), demonstrating the transition of G_0/G_1, S-phase, and mitosis fraction toward more benign pathology.

In our University Hospital, using flow cytometry we have developed a rapid cell-cycle protocol for intraoperative characterization of brain tumors and their margins (2). Since 2007 we have examined 56 neoplasms (21 gliomas, 25 meningiomas, 9 metastases, and 1 primary central nervous system lymphoma), and have shown that by analyzing G_0/G_1 phase, S-phase, and mitoses fraction, high-grade tumors could be distinguished from low-grade tumors (3). Furthermore, tumors' margins could be accurately assessed in gliomas (Fig. 1). The equipment for cell-cycle analysis is widely available and of low cost. Additionally, cell-cycle analysis is operated independently of pathology evaluation and can be interpreted easily.

We have recently proposed the integration of a flow cytometer with the Cavitational Ultrasonic Surgical Aspirator (CUSA), a widely used dissecting system that allows rapid and effective tumor removal. A recent study showed that tumor cells could be analyzed by flow cytometry and isolated from the liquid CUSA fraction (4). Apart from that, we have reported that cell-cycle analysis has an additional prognostic significance. Glioma patients with G_0/G_1 value lower than 69% and S-phase value greater than 6% were associated with worse survival (3). In conclusion, cell-cycle analysis by flow cytometry is a promising low-cost, widely available adjunct for intraoperative brain removal and should be further investigated.

George Vartholomatos[a], George Alexiou[b,c,1], Anna Batistatou[d], and Athanasios P. Kyritsis[c,e]

[a]Hematology Laboratory, Unit of Molecular Biology, [b]Department of Neurosurgery, [d]Department of Pathology, [e]Department of Neurology, and [c]Neurosurgical Institute, University Hospital of Ioannina, Ioannina, 45500, Greece

1 Santagata S, et al. (2014) Intraoperative mass spectrometry mapping of an onco-metabolite to guide brain tumor surgery. *Proc Natl Acad Sci USA* 111(30):11121–11126.
2 Alexiou GA, et al. (2014) Fast cell-cycle analysis for intraoperative characterization of brain tumor margins and malignancy. A pilot study. *J Clin Neurosci*, 10.1016/j.jocn.2014.05.029.
3 Alexiou GA, et al. (2013) DNA content is associated with malignancy of intracranial neoplasms. *Clin Neurol Neurosurg* 115(9): 1784–1787.
4 Day BW, et al. (2013) Glioma surgical aspirate: A viable source of tumor tissue for experimental research. *Cancers (Basel)* 5(2):357–371.

Author contributions: G.V., G.A., and A.P.K. designed research; G.V. and G.A. performed research; G.V. contributed new reagents/analytic tools; G.V., G.A., A.B., and A.P.K. analyzed data; and G.A. and A.B. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. Email: alexiougr@gmail.com.