Glioma resection and tumor recurrence: back to Semmelweis.

David Ratel, Boudewijn Van Der Sanden, Didier Wion

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It is difficult to believe that in the twenty-first century a medical procedure could contribute to the relapse of the disease it was intended to treat. Medical practices such as bloodletting are definitely behind us now. Furthermore, thanks to Semmelweis,[1,2] puerperal fever, which was transmitted by the contamination of surgeons' hands after they left autopsy rooms, has disappeared.

Gliomas are brain tumors that locally invade the brain parenchyma. Surgical excision is the proposed first-line therapy. Compelling evidence demonstrates that glioma resection improves overall survival, as well as the superiority of gross total resection over subtotal resection and biopsy.[3,4] In a previous issue of *Neuro-Oncology*, Lemée et al[5] discussed the fact that almost invariably patients die because of local recurrence at the margins of tumor resection. Now, in a recent issue of *Neuro-Oncology*, Okolieet al[6] demonstrate that in a murine glioma resection and recurrence model, injury to astrocytes promotes tumor proliferation and migration in vitro. This work is important for at least 2 reasons: (i) it points to a role of surgical brain injury (SBI) in tumor recurrence and (ii) it offers opportunity for epistemological considerations.

Prior to the work of Okolie et al, there was not much concern about the cause of glioma recurrence in the postsurgical tumor microenvironment. Tumor resection is necessary and extends overall patient survival.[3,4] It seems obvious that tumors would recur in the resection margin, as most of the residual cancer cells are located there. A largely overlooked point is that glioma resection, whether it is gross total resection or subtotal resection, causes lesion.[7] The response to SBI and its possible contribution to glioma recurrence have not been thoroughly investigated.7 The response to accidental CNS damage has been better studied.8 This response involves reactive gliosis, inflammation, and angiogenesis. Given what we know about the CNS response to accidental trauma, the brain response to glioma resection is likely to be a complex and dynamic process with both protumorigenic and antitumorigenic features that vary over time and space.7 Hence, residual glioma cells left in the regions surrounding the lesion core can hijack some components of the surgery-induced healing response to trigger tumor regrowth.[7] Reactive astrocytes are now identified as one of these recurrence-promoting factors induced by surgery.[6]

A key point we want to address here is that brain tumor resection is performed daily in patients without any further investigations of its side effects on the recurrence of the disease it is intended to treat. This does not question the importance of glioma surgery to reduce tumor burden and prepare for adjuvant therapy. Nevertheless, this lack of consideration raises concerns about why we have overlooked what is actually happening in

and around the resection margin for such a long time. Indeed, we might have been unconsciously reluctant to address this concern for the same reasons it was difficult to accept that contamination transmitted via surgeons' hands could spread puerperal fever in Semmelweis' time.[1,2] In 1847, washing hands did not fit well with the conceptual frameworks of reference for puerperal fever. Three decades later, Louis Pasteur and Robert Koch provided the adequate corresponding theoretical frame, namely the germ theory of disease. As Sir Peter Medawar remarked in his book *Pluto'sRepublic*, "[W]e scientists often miss things that are staring us in the face because they do not enter into our conception of what might be true." A phenomenon acquires meaning when it enters into the framework of a theory, but preexisting paradigms and theoretical commitments can also bias our observations.[9] Experimental and medical protocols may gradually become rituals. As regards glioma recurrence at the resection margin, accumulative evidence suggests that the tissue response to SBI participates in the formation of recurrence-prone microenvironments.[6,7] The matter now is to gather these clinical observations and experimental evidences in a testable unifying paradigm in such a way that the role of SBI in tumor recurrence "enters into our conception of what might be true." Fuller integration of such considerations would probably have accelerated the awareness on the role of SBI in glioma recurrence. To establish effective treatment against cancer recurrence, we must consider that our medical procedures can participate in tumor recurrence by creating tumorigenic microenvironments. Cancer surgery is certainly more than just the excision of a tumor mass,[6,7,10–12] and we have to learn more from Semmelweis than just a lesson on asepsis.

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