**Neurosurgical forum**  
**Letters to the editor**

**Extended endoscopic endonasal approach**

To The Editor: I have taken a great interest in the recently published article by Di Maio et al. (Di Maio S, Cavallo LM, Esposito F, et al: Extended endoscopic endonasal approach for selected pituitary adenomas: early experience. Clinical article. *J Neurosurg* 114:345–353, February 2011), which reported the result of management of selected pituitary adenomas, using an extended endoscopic endonasal approach. The authors presented convincing evidence that such treatment confers greater benefits, as compared with the standard approach. Initial results are promising and may justify a widening of the current classical indications of transsphenoidal surgery for this kind of pituitary adenoma.

As I have a special interest in articles that bear on the transnasal approach to the skull base, I was most interested in reading this article, and above all particularly honored to have been quoted on a number of occasions in the article.

Indeed, I would like to express my gratitude to the authors. However, I was slightly disappointed to notice that my surgical contribution in performing many of the 92 extended procedures, reported in the article, has been neglected. Indeed, I respectfully point out, just for the pursuit of truth, that the majority of patients have undergone extended endonasal surgeries at the Neurosurgical Department of Federico II University of Naples, between 2003 and 2008 (when I retired), carried out by myself together with Dr. Cavallo (such a tandem surgery needs 2 surgeons to perform a “four hand technique”). It is easily provable by reading what is reported in the papers of references 19 and 21 cited in *Patients and Methods*, where surgeons are indicated, in contrast to what is reported in the Results of the present article, where the authors state: “...92 EEEAs have been performed by the senior authors... (L.M.C., P.C.).” In such a way they lead to a misconception because this information, in reality, does not adhere to the truth.

Nevertheless, I’m sure that it was a misunderstanding, maybe due to a mere oversight on the part of the authors. Otherwise, it would be quite disconcerting, particularly for the fact that 2 of the authors, serving as my alumni, have shared with me, right from the start, the exciting experience of the evolution of endoscopic endonasal pituitary and skull base surgery. Finally, while I congratulate the authors on this timely and excellent paper, which is likely to be very influential, I would exhort them not to neglect Newton’s old aphorism: “*nos quasi nanos gigantium humeris insidientes*” (we are as dwarfs on the shoulders of giants, and can see far..., for we have been lifted high by their gigantic grandeur).

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**Disclosure**

The author reports no financial conflict of interest.

Response: We regret that we did not make clear that some of the patients in the reported cases were operated upon by Dr. de Divitiis. As the former Chair of the Department of Neurosurgery, he helped to lead the way in establishing the concepts and realization of endoscopic approaches to sellar and parasellar anterior skull base lesions. This is clear from our citations of his prior work (references 17–22) in our paper, which is the product of his previous leadership and support.

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**Brain edema**

To The Editor: We are interested in the laboratory investigation by Ellis et al. (Ellis TL, Garcia PA, Rossmeisl JH Jr, et al: Nonthermal irreversible electroporation for intracranial surgical applications. Laboratory investigation. *J Neurosurg* 114:681–688, March 2011). We propose dissecting the molecular mechanism of brain edema after treatment with nonthermal irreversible electroporation (NTIRE).

Nonthermal irreversible electroporation is a novel, promising method for the ablation of tumors. Ellis et al.1 conducted a laboratory study on the treatment of canine brain tumor using NTIRE to insert blunt-tipped electrodes into the brain and tumor tissue after craniotomy. They showed tumor destruction on histopathological sections and brain edema on MR images.

Some limitations exist in their study. First, the corresponding histological section showed tumor destruction in the NTIRE-treated area. Second, evidence of worsening brain edema after the NTIRE application was proven on MR imaging of the brain. From dissection of the molecular mechanism arose the concern of releasing more intracellular proteins, such as matrix metalloproteinases-2,3 osteopontin,4,5 vascular endothelial growth factor (VEGF),2 and Nodal2,4 into the intercellular space when using NTIRE to create holes in cancer cells. Vascular endothelial growth factor has been reported not only to promote brain edema, but also to increase angiogenesis when host cells sense the VEGF release from cancer cells.5,6 Moreover, since NTIRE itself did not affect the thermal change, protein release from the intracellular space would not be completely damaged. We propose that NTIRE
lysed tumor cells and released proteins, suggesting one of the possible mechanisms contributing to brain edema. Since brain-occupying lesions increase intracranial pressure and worsen neurological status, it is very important to overcome the issue of brain edema in clinical treatment. Despite these minor limitations, the authors' study has provided evidence of a potential therapeutic application. Further studies are necessary before translation into clinical human application.

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Disclosure

The authors report no conflicts of interest.

References


RESPONSE: We appreciate the opportunity to respond to the letter that proposes a hypothesis for the mechanism of brain edema in NTIRE. The letter by Hueng and Sytwu was written in response to a laboratory investigation in which we evaluated the safety of an NTIRE procedure to lesion normal canine brain tissue.

First of all, we thank Drs. Hueng and Sytwu for their interest in the NTIRE investigation and for their letter. We believe that deepening our understanding of the mechanisms of NTIRE-induced tissue ablation as well as brain edema is important and agree that further studies are necessary before translation into clinical human applications.

In terms of the minor limitations described by Hueng and Sytwu, we would like to point out that our study only examined the effects of NTIRE in a limited region of normal canine brain. As described in the references provided by Hueng and Sytwu and in other studies by our group, there is a low constitutive VEGF expression in the normal brain as compared with that in tumors. Consequently, the contribution of VEGF in the formation of vasogenic edema in normal brain might not be a major factor, especially since major vasculature is spared in NTIRE treatments. However, as Drs. Hueng and Sytwu indicate, there are numerous other potential mediators of vascular permeability that may contribute to the edema observed following NTIRE treatment that deserve further investigation.

Additionally, we have recently published the first clinical application of NTIRE for the treatment of an inoperable, spontaneous, malignant intracranial glioma in a canine. In that study we were able to safely and successfully ablate the brain tumor without exacerbating edema, hemorrhage, or intracranial hypertension. These results, as well as data from other canine gliomas treated in an active NTIRE clinical trial, suggest that NTIRE-associated brain edema, while deserving of clinical concern, is mild and amenable to pharmacological therapy, and thus will not be a limiting factor in future therapeutic applications of this technology.

Thank you again for your interest in our laboratory investigation.

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Disclosure

Dr. Davalos holds a patent with AngioDynamics.

References


Severe disability