Head Injury and Therapeutic Hypothermia

TO THE EDITOR: Marion, *et al.* (Marion DW, Obrist WD, Carlier PM, et al: The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg 79:*354–362, September, 1993), and Shiozaki, *et al.* (Shiozaki T, Sugimoto H, Taneda M, et al: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg 79:*363–368, September, 1993), were admirably cautious in not drawing the inference that mild hypothermia improves outcome for patients who have suffered severe head injury. At the same time, they did not draw the opposite conclusion, noting that their respective preliminary results showed a positive trend, and that their sample sizes were too small to warrant a negative inference — again, an appropriate level of restraint and an entirely justified suggestion.

However, since both groups of investigators used comparable patients, the same outcome measure, and nearly identical levels of hypothermia, it would not be unreasonable to combine their Glasgow Outcome Scale (GOS) results and analyze those findings with a Mann-Whitney U-test (as distinct from the chi-squared test used by Marion, *et al.*, which would not utilize the information that the GOS is an ordinal or ranked scale). That test yields a two-tailed p value of 0.0236, indicating even stronger support for "the initiation of a multicenter trial of therapeutic moderate hypothermia for the treatment of severe closed head injury" as suggested by Marion, *et al.*

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RESPONSE: I appreciate Dr. Hartung analyzing the clinical outcomes in our study together with the outcomes in the study by Shiozaki, *et al.*[1] However, it should be emphasized that the hypothetical bases for the two studies were quite different. Our study was designed to determine if moderate hypothermia would alleviate early secondary brain injury that ultimately leads to posttraumatic brain swelling, while the Shiozaki study was aimed at determining if hypothermia would reduce brain swelling that has already occurred. Therefore, the intracranial pressure at the time of initiation of hypothermia was much lower in our patients than it was in the subjects of the Shiozaki study. Cooling of our patients was begun much sooner after injury and was continued for only 24 hours, rather than the 48 hours or more described for the Shiozaki study. The criteria for eligibility of patients in the two studies also differed: we used the patient's initial Glasgow Coma Scale score and computerized tomography findings, whereas the Shiozaki study included only patients with intracranial hypertension refractory to barbiturate therapy.

For these and several other reasons it is likely that there were substantial differences between the two studies in the types and severity of head injury suffered by the subjects. Although it is interesting that hypothermia had positive effects in both groups of patients, combining the two series is, in our view, not scientifically valid. Proof of the efficacy of therapeutic moderate hypothermia will depend on the results of a multicenter trial that is tightly controlled, uses the same randomization criteria and treatment protocols, and addresses the same hypothesis.

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Reference

1. Shiozaki T, Sugimoto H, Taneda M, et al: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. **J Neurosurg 79:**363–368, 1993

Biopsy of Low-Grade Astrocytomas

TO THE EDITOR: We support the observation made by Kondziolka, *et al.*, that the predictive value of preoperative imaging regarding histology of presumed low-grade astrocytoma is limited (Kondziolka D, Lunsford LD, Martinez AJ: Unreliability of contemporary neurodiagnosis imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma. *J Neurosurg 79:*533–536, October, 1993). They found that 50% of 20 lesions considered preoperatively to be low-grade astrocytomas were indeed something else. Of 48 stereotactic biopsies we have performed on patients with compelling preoperative clinical and neuroimaging diagnosis of low-grade astrocytoma, 15 lesions (31.3%) proved to be something else. Six were astrocytoma of higher grade, six were oligodendroglioma or mixed astrocytoma-oligodendroglioma, and three were inflammatory lesions.

However, we disagree that this observation leads to the conclusion that every brain lesion suspected of being a low-grade astrocytoma requires a biopsy. This is certainly the case if therapy (resection and/or radiation) is thought to be indicated. However, if 1) the neuroimaging and clinical picture are compatible with low-grade astrocytoma, 2) the lesion does not require treatment in the judgment of the clinician because the patient is well (for example, an intact patient with seizures only), 3) the lesion has not produced mass effect, and 4) the clinician subscribes to the school of thought in which one does not know if there is unequivocal benefit of "up-front" surgery and/or radiation for low-grade astrocytoma,[2] then a course of simple observation is still an acceptable approach. Simple observation includes repeat imaging at an early interval (such as 2 months) after initial assessment and at regular intervals thereafter. If the lesion is an astrocytoma of higher grade, this will be detected by subsequent changes on neuroimaging and/or in the clinical status of the patient, and treatment will be undertaken at that time (there is no evidence to suggest that delaying therapy is detrimental to patient outcome).

In favor of a course of observation over biopsy in selected cases is the risk of a biopsy-related complication in a situation where therapy may not be dictated by the results of the biopsy. The complication rate in

the 20 patients described by Kondziolka was 0%, but two (4.2%) of our 48 patients were worsened by biopsy of low-grade astrocytoma (one suffered a devastating intracerebral hemorrhage and one a mild subarachnoid hemorrhage). The complication rate of stereotactic biopsy ranges up to 7% in some large series,[1] but is admittedly probably lower in lesions of low grade histologically. Furthermore, the biopsy is not even guaranteed to reliably confirm the histological grade because of the potential for sampling error in the lesion due to histological heterogeneity common within glial neoplasms, especially when there is no enhancement to guide the surgeon to the highest-grade region of the tumor.

In summary, if a clinician believes that every supratentorial low-grade astrocytoma must be treated *ab initio* (and we do not presently have scientific evidence to support this belief),[2] then stereotactic (or excisional) biopsy is required prior to therapy. If a clinician considers that some low-grade astrocytomas do not require treatment *ab initio* (and we do not presently have scientific evidence to support this belief either), then close monitoring of clinical and imaging data can be safely undertaken and treatment instituted at the first sign of change in the brain lesion. It would appear that the only scientifically justifiable reason for a neurosurgeon to perform stereotactic biopsy on every patient suspected of harboring a supratentorial low-grade astrocytoma is his/her participation in a randomized study comparing treatment approaches in these patients.

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References

1. Mundinger F: CT stereotactic biopsy for optimizing the therapy of intracranial processes. **Acta Neurochir Suppl 35:**70–74, 1985
2. Recht LD, Lew R, Smith TW: Suspected low-grade glioma: is deferring treatment safe? **Ann Neurol 31:**431–436, 1992

RESPONSE: We thank Drs. Bernstein and Guha for their pertinent comments on this issue. The data from their own series agree with the central conclusion of our paper: high-quality neuroimaging studies alone are often unable to confirm the diagnosis of low-grade astrocytoma.

The authors emphasize that many physicians currently do not believe that every lesion suspected of being a low-grade astrocytoma should undergo a biopsy. They argue that some patients with low-grade astrocytoma may not require any treatment other than anticonvulsant medication, as guided by their clinical and imaging presentation. However, they state that in their series, 31% of patients proved not to have a low-grade astrocytoma, since six had high-grade glial neoplasms and three had inflammatory lesions. Taking the nonbiopsy approach in their series alone, nine patients would be managed inappropriately by imaging criteria. They argue that a delay in diagnosis may not be detrimental. We believe that delay in the treatment of a tumor (astrocytoma) with a reported median survival range of 5 to 10 years (certainly not a benign clinical outcome), can hardly be justified in the 1990's.

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Postoperative Irradiation for Meningiomas: Erratum

We wish to point out a typographical error in a reference citation in the recent article by Goldsmith, *et al.* (Goldsmith BJ, Wara WM, Wilson CB, et al: Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *J Neurosurg 80:*195–201, February, 1994). On page 195, line 14 in the left column, references 11 and 13 are cited in error; instead, references 1 and 3 should have been cited. We regret the error. — EDITOR