Our panel of experts highlights the most important research articles across the spectrum of topics relevant to the field of CNS oncology

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Alford R, Gargan L, Bowers DC, Klesse LJ, Weprin B, Koral K. Postoperative surveillance of pediatric cerebellar pilocytic astrocytoma. *J. Neurooncol.* doi:10.1007/s11060-016-2222-x (2016) (Epub ahead of print)

The interest of this paper is the discussion about the necessity of radiological follow-up in cerebellar pilocytic astrocytomas (CPAs), especially those that were confirmed as completely operated at diagnosis. The problem of the usefulness of strict follow-up is of interest in many oncologic diseases, and doubts on significance and timing of radiological examinations have been aroused also for malignant brain tumors. In this case, the authors have started from the point of verifying when and how often a postoperative surveillance needs to be performed, considering the disadvantages of a potential patient and family stress, possible anesthesia need, and public and private costs. The authors' hypothesis was that following two MRI examinations, separated by at least 3 months, showing no evidence of tumor, gross totally resected CPAs did not recur and no further imaging follow-up was necessary. After a retrospective review of 53/222 low-grade tumors of their patients in nearly 13 years, they could confirm their hypothesis that two negative consecutive MRIs spaced ≥ 3 months proved to correspond to a very low likelihood of future recurrence in CPAs. These results may serve

as a good cut-off point to transition to a less-frequent surveillance imaging protocol in this specific patient population. An adequate follow-up in the immediate postoperative period, and when suspicious findings are present, is needed, but the unnecessary risks and costs of excessive long-term imaging can be eliminated.

Written by Maura Massimino

Greenfield JP, Castañeda Heredia A, George E, Kieran MW, Morales La Madrid A. Gliomatosis cerebri: a consensus summary report from the First International Gliomatosis Cerebri Group Meeting, 26–27 March 2015, Paris, France. *Pediatr. Blood Cancer* doi:10.1002/pbc.26169 (2016) (Epub ahead of print)

The subject of the meeting, whose conclusions are here reported, was the clinical, radiologic and morphologic diagnostic criteria (with an emphasis on the diagnostic procedures and tissue manipulation), the pediatric therapeutic recommendations and the relevant collaborative pre-clinical projects on gliomatosis cerebri (GC). GC was defined as a diffuse glioma with an extensive infiltration of a large region of the CNS with the involvement of at least three contiguous cerebral lobes. It usually has bilateral involvement of the cerebral hemispheres and/or gray matter, with frequent extension to the brain stem, cerebellum

and even – although less frequently – the spinal cord. Type 1 is the most frequent variant and consists in diffuse neoplastic growth while type 2 is characterized by a more obvious mass in addition to the diffuse component. Although the 2016 WHO classification has erased GC, this has a distinct entity because of lack of specific molecular subgroup; still no agreement exists on the therapeutic conduct because of the rarity and severity of this condition. Since there is no effective therapy for GCs, it is important to identify immunohistochemical, molecular, genomic and epigenomic markers. The heterogeneity of the entity is demonstrated by the few molecular data gathered showing 10% incidence of mutations in H3.3G34 and H3.3K27 and mutations in SETD2 (20%), EGFR (30%) and p53 (40%). Before a common consensus on therapeutic guidelines can be pronounced, the clinical recommendations are toward the same treatment as for the other high-grade glioma including irradiation. Obviously, any target therapy must be based on the most recent and representative tumor/tumors biopsy.

Written by Maura Massimino

Gokce-Samar Z, Beuriat PA, Faure-Contier C et al. Preradiation chemotherapy improves survival in pediatric diffuse intrinsic pontine gliomas. *Childs Nerv. Syst.* 32(8), 1415–1423 (2016)

The authors bring to our attention the 10-year experience at Léon Berard Oncologic Center with diffuse intrinsic pontine glioma. In the present era, as we have had the opportunity to comment in these pages, a great amount of knowledge has been gathered about the biology of this entity, discovered and validated through tumor tissue processed after postmortem examination or after pretreatment biopsy. The biopsy procedure has been exported into many centers and is claimed as very safe. The ethical issue of its usefulness is very strong and more diffuse recommendation gives biopsy indications only in the context of an approved clinical protocol, this means, only if, of potential utility to drive treatment. How this potentiality realizes is the subject of the paper. The authors reviewed retrospectively the outcome of 25 cases: 16, already published in a previous paper, treated with an ‘old-fashioned’ approach with chemotherapy first followed by radiation at relapse [1]. Preradiation chemotherapy may improve survival in pediatric

diffuse intrinsic brainstem gliomas: final results of BSG 98 prospective trial [1] and 9 put into ‘innovative’ protocols with target therapy after biopsies. Three of nine of the second group had severe complications after biopsy that prevented their planned treatment and their overall survival was significantly lower than in the chemoradiotherapy group. This means that, despite ongoing clinical trials investigating a wide array of targeted therapies, no clear benefit from any modality apart from radiotherapy has yet been demonstrated, and, as the authors correctly underline, the biopsic procedure that is now compulsory in many protocols can be interpreted as a paternalistic attitude that may offend some families, who may feel deprived of their rights without seeing real benefits to biopsy. The issue of providing tissue to have a deeper genetic and molecular knowledge of diffuse intrinsic pontine glioma must not be confused with the success of an innovative approach because of a supposed ‘target’ therapy.

Written by Maura Massimino

Ramaswamy V, Hielscher T, Mack SC et al. Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: a retrospective multicohort analysis. *J. Clin. Oncol.* 34(21), 2468–2476 (2016)

Posterior fossa ependymomas are two distinct molecular entities, EPN_PFA which have increased methylation and EPN_PFB which lack this feature. The authors studied 820 cases collected from four sources (PFA 678 and PFB 142). In multivariate analysis, the PFA subtype was a strong predictor for worse survival (hazard ratio [HR]: 4.30). PFB tumors are generally in a midline location, more amenable to resection than PFA. Incomplete resection was a strong negative predictor of survival (HR: 2.05 for PFA and 11.32 for PFB). For the PFA group, median age was 3 years, and 92% were <10; survival was worse for men (HR: 1.39). For PFA tumors, first-line radiotherapy (RT) was beneficial for survival by multivariate analysis (HR: 0.52), but the outcome was sufficiently poor for subtotally resected PFA tumors that the authors recommend clinical trial entry rather than RT. For the PFB group, age was <10 in 8%, 10–17 in 25%, and 18 and older in 67% of patients. Gross totally resected PFB tumors have an excellent prognosis (survival >85% at 10 years), and

for these, the authors recommend observation without RT.

– Written by Larry Junck

Wang J, Cazzato E, Ladewig E *et al.* Clonal evolution of glioblastoma under therapy. *Nat. Genet.* 48(7), 768–776 (2016)

The authors analyzed whole exomes of 93 glioblastomas and transcriptomes of 65 at initial diagnosis and recurrence. Seventeen patients, all treated with temozolomide, acquired hypermutation (>500), and 16 of them gained mutations in mismatch repair (MMR) genes, notably MSH6. Patients with hypermutation survived a median of 24 months, slightly more than those without hypermutation. In 57% of patients, mutations occurring in only one of a patient's samples outnumbered those shared in the two samples. In 54/92 patients, at least four clonal mutations at diagnosis were lost at recurrence; these and other findings suggest that the recurrence was not a subclone of the clone at initial diagnosis but originated from a common ancestor clone, diverging more than a decade earlier. Transcription subtypes changed at recurrence, more often in primary glioblastoma (39/58) than in secondary tumors (2/7). The data suggest that mutations in *IDH1*, *PIK3CA* and *ATRX* are early events; those in *TP53*, *NF1* and *PTEN* occur later; and those in *MSH6* and *LTBP4* (10/93 cases) are relapse specific. *LTBP4* encodes a protein that binds to TGF- β , which is known to drive tumor growth. The authors found that silencing *LTBP4* in two cell lines decreases expression of TGF- β target genes and decreases cell proliferation,

thus identifying *LTBP4* as a potential target for treatment.

Written by Larry Junck

Brown PD, Jaeckle K, Ballman KV *et al.* Effect of radiosurgery alone versus radiosurgery with whole brain radiation therapy on cognitive function in patients with one to three brain metastases. A randomized clinical trial. *JAMA* 316(4), 401–409 (2016)

For patients with one to three metastases, adding whole-brain radiation (WBRT) to stereotactic radiosurgery (SRS) is known to improve tumor control but add toxicity. Whether this provides net benefit is unclear. In this trial, 213 patients at 34 centers with one to three metastases of <3 cm in size were randomized to receive SRS with or without WBRT (30 Gy in 12 fractions). Time to intracranial progression was shorter for SRS alone (hazard ratio: 3.6; $p < 0.001$), but survival was similar in the two groups (hazard ratio: 1.02, not significant). Quality of life was higher at 3 months with SRS alone (-0.1 vs -12.0 points). For 12-month survivors, cognitive deterioration was less common after SRS alone at 3 months (5/11 vs 16/17; $p = 0.007$) and at 12 months (6/10 vs 17/18; $p = 0.04$). The authors suggest that for patients with one to three metastases amenable to radiosurgery, SRS alone may be preferable to combined treatment.

Written by Larry Junck

Reference

- 1 Frappaz D, Schell M, Thiesse P *et al.* Preradiation chemotherapy may improve survival in pediatric diffuse intrinsic brainstem gliomas: final results of BSG 98 prospective trial. *Neuro Oncol.* 10, 599–607 (2008).