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

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Upadhyaya SA, Ghazwani Y, Wu S et al. Mortality in children with low-grade glioma or glioneuronal tumors: a single-institution study. *Pediatr. Blood Cancer* doi:10.1002/pbc.26717 (2017) (Epub ahead of print).

The interest of this paper lies in the kind of worries that their authors arise with respect to features of long-term negative outcome in a series of low-grade gliomas treated at St Jude's Hospital during a 30-year time span, until 2015. Of the 87 patients among 727 with low-grade glioma coming to death and representing the 12% of the whole cohort, they have highlighted the main clinical features. The most common site of disease was midbrain/thalamus and the most common cause of death was progressive disease after a median 4 years. What is less obvious is that the second cause of death was the progression of high-grade glioma being both a second tumor after irradiation and a spontaneous progression of previously low-grade glioma. Among this last group of 15 patients, death could occur as late as after 10 years from diagnosis. Not having whole genome analysis, it remains to be understood if these high-grade tumors were due to treatment, in other words, radiation therapy or were consistent with aggressive mutations like H3k27 that can be found in midline glial tumors.

Another notable aspect is the death for suicide in four patients that gives a clue on how difficult could be the management of such chronic diseases both for clinicians and patients with possibly many episodes of progressive disease and a continuous alert on imaging.

In summary we reflect again that such 'benign' diseases may mine the future of our patients for many years and they must be followed and sustained for a very, very long period of time.

– Written by Maura Massimino

Veldhuijzen van Zanten SE, Baugh J, Chaney B et al. Members of the SIOPE DIPG network. Development of the SIOPE DIPG network, registry and imaging repository: a collaborative effort to optimize research into a rare and lethal disease. *J. Neurooncol.* 132(2), 255–266 (2017).

Among the many efforts that all the pediatric neuro-oncology community is doing to ameliorate the dismal prognosis of children with DIPG, two registries were created. One is mostly USA, Australia and Canada based, the other European, but probably soon also including Turkey and Mexico patients. The registration does not mean only the inclusion of demographic data, but also imaging, treatment, histopathological and biological analyses, when available, in a retrospective and prospective modality. The registries will be able to put more light on this ominous disease through the grouping of patients with similar/different features, protocol and outcome. Biometric models will be applied. The registries will be maintained during time mainly with charities foundation. This paper reports the story of the birth of the SIOPE registry that is now extended also to Russia, Turkey and Mexico with the presence of an executive committee, a group of scientific advisors, national coordinators and members. The collection of data is web-based and there are already some international studies done and published and some other

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in the pipeline, like that of long-term survivors to be compared with all the other patients. At the moment of the paper publication, data on nearly 700 patients have been already put in the SIOPE registry.

– Written by Maura Massimino

Veneroni L, Boschetti L, Barretta F et al. Quality of life in long-term survivors treated for metastatic medulloblastoma with a hyperfractionated accelerated radiotherapy (HART) strategy. *Childs Nerv. Syst.* doi:10.1007/s00381-017-3548-1 (2017) (Epub ahead of print).

This paper represents one of the very few reports on quality of long-term survivors in a cohort of children and adolescents homogeneously treated for metastatic medulloblastoma. Clinical results were already published in 2009 [1] and were and remain among the best for this patients subgroup, but it was necessary to know also functional patients outcome. The authors thus have launched a study on 33 patients surviving at least 3 years to understand their actual conditions. Patients were asked to complete self-administered quality of life questionnaires analyzing different functional scales for different ages, and authors, based on patients' clinical data, created an index (called IPI index, i.e., index of physical impairments) to obtain an overall objective measure of patients' physical impairments at the time of questionnaires filling. Six major sequelae were reported in six scales (alopecia, epilepsy, endocrine disorders, hearing loss, walking disabilities and visual deficits), divided in three levels each (absent, mild/compensable, or severe). Of the 25 patients completing all what required after a median of over 12 years from treatment, 19 were modestly impaired (LI group) and six were severely impaired (HI group). Quality of life, in general, was not severely impaired possibly due to a compensatory effect in the form of a psychological defense mechanism of emotional and social adaptation even if HI group reported a worse physical, social, daily and cognitive functioning than patients in the LI group. This paper also underlines that many patients received social support in special education services, tailored rehabilitation programs and sports activities, programs to help them socialize with peers and economic support too, and this is mandatory when planning treatment for such a severe disease that requires intensive treatment to reach patients cure.

– Written by Maura Massimino

Northcott PA, Buchhalter I, Morrissy AS et al. The whole-genome landscape of medulloblastoma subtypes. *Nature* 547(7663), 311–330 (2017).

The authors studied medulloblastoma samples including sequencing of whole genome in 390 (some previously reported in less detail), whole exome in 101 (previously published) and epigenetic methylation array in 1256. Using more advanced approaches, they were able to find many more driver mutations than have been found previously. Among the four subgroups, candidate drivers were found in 100% of WNT tumors, >95% of SHH, 76% of Group 3 and 82% of Group 4. Most driver mutations were of low frequency (<5% of samples), mutually exclusive (one per sample), limited to one subgroup and clonal (estimated cell fraction, 1.0). Mutations of special interest were in-frame insertions in KBTBD4 (18 patients, groups 3 and 4) and enhancer hijacking mutations activating PRDM6. Six tumors in the SHH subgroup had IDH1 R132C mutations, all in tumors manifesting the CpG island methylator phenotype (CIMP+). Genetic events involving histone modifiers were common across subgroups, tumors in Group 3 and Group 4 had methylation that could be categorized into eight subtypes and some somatic mutations corresponded to a specific methylation subtype. The molecular underpinnings of medulloblastoma are proving to be complex and varied.

– Written by Larry Junck

van den Bent MJ, Baumert B, Erridge SC et al. Interim results from the CATNON trial (EORTC study 26053–22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a Phase III, randomized, open-label intergroup study. *Lancet* doi:10.1016/S0140-6736(17)31442-3 (2017) (Epub ahead of print).

This article reports the interim analysis of a Phase III randomized study of newly diagnosed noncodeleted anaplastic gliomas. Patients were randomized using a 2 × 2 factorial design to receive radiation (59.4 Gy in 33 fractions), with or without concurrent temozolomide, with or without adjuvant cyclic temozolomide to follow. A total of 745 patients were entered and 219 deaths had occurred. Patients were stratified by institution, performance status, age, 1p loss of heterozygosity (yes vs no), oligodendroglioma features and MGMT promoter methylation status.

Survival adjusted for stratification factors, the primary endpoint, was significantly better with concurrent temozolomide with HR: 0.65 (99% CI: 0.45–93). At 5 years, survival was 55.9% with temozolomide versus 44.1% at

without; progression-free survival was 43.1 and 24.3%, respectively. Further analysis, including analysis of benefit associated with concurrent temozolomide, awaits longer follow-up.

– Written by Larry Junck

Alattar AA, Brandel MG, Hirshman BR et al. Oligodendroglioma resection: a surveillance, epidemiology, and end results (SEER) analysis. *J. Neurosurg.* doi:10.3171/2016.11.JNS161974 (2017) (Epub ahead of print).

As background, patients with primary CNS lymphoma, a highly treatment-responsive tumor, are thought not to benefit from resection in most cases. Oligodendroglioma is a fairly treatment-responsive tumor, and the authors explored the possibility that it also may not benefit from resection. Using the Surveillance, Epidemiology and End Results database, the authors compared the survival following gross total resection (GTR), subtotal resection (STR) and biopsy only in 2378 patients with WHO grade II oligodendroglioma (O2) and 1028 patients with WHO grade III oligodendroglioma (O3), with adjustment for demographics and clinical covariates. Among O2 patients, the hazard of death was 1.06 for GTR and 1.21 for STR, compared with patients undergoing only biopsy. Among O3 patients, hazard of death was 1.18 for GTR and 1.62 for STR, compared with biopsy only. An important limitation is that the survival end point analyzed was the time at which survival dropped to 75%; use of this end point may capture nearly all the morbidity of resection but only a fraction of its potential benefit. Additional limitations include the absence of adjustment for co-deletion or IDH mutation, also that determination of GTR versus STR was only from postoperative radiology reports. Nonetheless, the authors have introduced an interesting new concept, supported by analysis including a large number of patients.

– Written by Larry Junck

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