Adult Medulloblastoma, From Spongioblastoma Cerebelli to the Present Day: A Review of Treatment and the Integration of Molecular Markers

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Here we present the history, staging system, and treatment of medulloblastoma, reviewing the prognostic value and clinical application of molecular subtyping while highlighting the differences between adult and pediatric disease.

Introduction

Almost 90 years ago, in June 1924, Harvey Cushing and Percival Bailey presented on the tumor “spongioblastoma cerebelli” at the American Neurological Association meeting, describing tumors they believed to arise from embryonal rests of undifferentiated cells within the roof and ependymal lining of the fourth ventricle.[1] Although “spongioblastoma” aptly described the soft, “suckable” gross surgical qualities of the tumor, they abandoned the title in favor of “medulloblastoma” based on a paper by Shaper in 1897 that suggested the medulloblast as one of five types of stem cells populating the primitive neural tube.[2,3] Cushing reported that his medulloblastoma patients had a mean age of 11 years, and while those with midcerebellar and vermis region tumors averaged 8.3 years of age, he noted that patients with lateral cerebellar hemispheric involvement had a much higher average age of 31 years.[1,4] This description was one of the first of several differences between pediatric and adult disease to be reported, although it was not consistently confirmed in other studies. Medulloblastomas are rare in adults, with an incidence of 0.5 per million, and comprise 2% of primary brain tumors in young adults between the ages of 20 and 34 years.[5] Children born prematurely have been noted to have a higher incidence of medulloblastoma (ratio 3.1); however, no environmental risk factors have been reliably identified.[6] Medulloblastoma is associated with several familial genetic syndromes, including Li-Fraumeni syndrome, Gorlin syndrome (nevoid basal cell carcinoma syndrome), Turcot syndrome, and Rubinstein-Taybi syndrome.[7] Clinical features include truncal ataxia, gait disturbances, and symptoms reflective of increased intracranial pressure caused by obstruction of cerebrospinal fluid (CSF): headaches, vomiting, and lethargy.

Staging

Unlike the majority of primary brain tumors in adults, medulloblastomas require staging, as they often disseminate along the neuroaxis. Medulloblastomas are “small round blue cell” tumors and have the capacity to behave in a highly invasive/metastatic manner. The majority of medulloblastomas originate within the posterior fossa, where they can infiltrate across the ependymal lining into the brainstem or “drop” into and disseminate within the CSF. Thus, staging requires complete imaging of the neuroaxis with magnetic resonance imaging (MRI) to exclude subarachnoid metastases, and a lumbar puncture for CSF cytology done either prior to surgery or at least 10 to 14 days afterwards, so that cells dislodged during surgery are not misinterpreted as truly disseminated disease.[8] Postoperative MRI of the brain within 24 to 48 hours should also be done to determine the extent of resection and the amount of residual disease.

TABLE 1
Chang Classification for Medulloblastoma

The Chang staging system (Table 1) was published in 1969 and denoted T stage, the size and invasiveness of the tumor at resection, as well as M stage, the extent of spread outside of the posterior fossa.[9] Patients with M0-1 and T1-2 disease fared best, and only 1 patient of 30 was denoted to have M2 or M3 disease.[9] In the present day, T staging does retain a prognostic role in adult medulloblastoma, as suggested in a prospective trial and in a large retrospective series.[10,11] M staging has shown prognostic importance in many studies, although some studies have not found a significant difference between M0 and M1 disease.[8,12,13] “Modified” Chang staging is the current standard and refers to the addition of imaging to stage these tumors, which were originally staged only surgically. Medulloblastoma is denoted as having greater or lesser risk, according to the likelihood of disease recurrence, although the terms associated with risk vary in the literature. Those in the better prognostic group have interchangeably been called “low risk,” “standard risk,” or “average risk,” and those in the poorer prognostic group are usually referred to as “high risk” or “poor risk.” To add further confusion, studies have varied in the parameters by which patients are assigned to risk groups. It is generally agreed that patients without metastases have a lower risk of recurrence, although the presence of postoperative residual disease as a prognostic factor is a matter of debate. In the pediatric literature, this appears to be true particularly for patients over 3 years of age with M0 disease, however, the most recent studies in adults have not shown a difference in survival for those with residual disease[11,12,14-21] (Table 2).

Pathology

TABLE 2

Characteristics of Adult and Pediatric Medulloblastoma

The most recent World Health Organization (WHO) classification was amended in 2007 and now recognizes five variants of medulloblastoma: classical, desmoplastic/nodular, medulloblastoma with extensive nodularity, anaplastic, and large-cell.[7] Medulloblastoma describes any variant with rhabdomyoblastic elements. The likelihood of hemispheric involvement increases with age, and some series showed a prevalence of desmoplastic/nodular histology.[7] Desmoplastic histology
generally is associated with a better outcome, while large cell/anaplastic histology is associated with a poor prognosis, although this has been demonstrated primarily in pediatric disease. Since the prognostic role of histology is controversial, in recent years specific molecular subtypes and key survival and growth pathways for these tumors (ie, sonic hedgehog [SHH] pathway-activated tumors) have been researched. Given their prognostic significance and potential to influence treatment in the era of molecularly targeted therapies, subtype analysis provides complementary information and may be more clinically relevant than histologic diagnosis alone.

### Molecular Subtyping

**TABLE 3**

| Overview of Molecular Subtypes of Medulloblastoma |

Recent advances in molecular genomics in the last decade have allowed for the comprehensive molecular profiling of medulloblastoma and other brain tumors. Two recent studies developed distinct molecular classifications of medulloblastoma seen in both children and adults, with implications for future molecularly targeted therapeutic clinical trials. Northcott and colleagues used integrative genomics to identify four specific molecular variants of medulloblastoma: WNT (wingless), SHH, Group 3, and Group 4. These four types have subgroup-specific demographics, histology, metastatic status, and DNA copy number aberrations (see Table 3; adapted from references 21–24). SHH tumors were seen in infants and adults, whereas WNT and Group 4 tumors were seen among patients of all ages.[22] In a separate analysis of adult medulloblastoma, Remke et al used gene expression profiling to reveal three distinct molecular variants, with distinct demographics, genetics, transcriptome, and prognostic implications: SHH, WNT, and subtype D. Both overall survival (OS) and progression-free survival (PFS) were superior for WNT-driven tumors and intermediate for SHH-driven tumors, while patients with subtype D tumors trended toward shorter survival times.[23] In the Northcott study, Group 3 tumors peaked in childhood, were not seen in adults, and conferred the poorest prognosis, independent of metastatic status.[22]

At a recent meeting, a consensus was reached to refer to the four subgroups as SHH, WNT, Group 3 (also known as subtype C), and Group 4 (also known as subtype D), in order to avoid confusion. While some studies have not found Group 3 tumors among adult cases, others have identified a very small percentage of Group 3 tumors representing less than 2% of all adult medulloblastoma cases.[24] The most common medulloblastoma subtype in adults is the SHH subtype, which accounts for 58% of all adult medulloblastoma cases—although interestingly, these tumors are genetically and transcriptionally distinct from childhood tumors with SHH pathway activation.[25] MYCN gene amplifications and 10q deletions are rare in this group compared with their incidence in pediatric SHH tumors. Group 4 represents 28% of adult medulloblastomas. WNT tumors occur less commonly, in approximately 13% of cases. Because of the inherent difficulty and expense of molecular profiling in real time, efforts are underway to translate tumor subtype identification using gene expression data into a more readily accessible technology such as immunohistochemistry (IHC). IHC for DKK1 (WNT), SFRP1 (SHH), NPR3 (Group 3), and KCNA1 (Group 4) could appropriately classify formalin-fixed medulloblastomas in about 98% of patients.[22] It is important that these subtype classifications have not been prospectively validated. Notably, subtype analysis may not be confidently determined using a single IHC marker per subtype. Given the molecular heterogeneity of tumors, multigene predictors using real-time polymerase chain reaction (PCR) on RNA isolated from formalin-fixed, paraffin-embedded (FFPE) samples may more reliably identify subtypes, and this procedure is routinely performed by the Radiation Therapy Oncology Group (RTOG) Brain Tumor group.

### Prognosis

Reliable outcome assessments are limited due to the small number of prospective clinical trials for
adult patients with medulloblastoma. In the past, prognosis has primarily been associated with certain demographic and clinical measures, and with tumor histology (see Table 2). Performance status postoperatively was not significantly associated with outcome in the only prospective study of adult medulloblastoma, which accrued patients from 1988 to 2001.[19] Two earlier studies had shown significantly more favorable outcomes for patients with ECOG (Eastern Cooperative Oncology Group) scores < 2.[20,21] Brandes and colleagues attributed this finding to improved surgical techniques in recent decades, as the studies by Frost and Carrie were done from 1958 to 1988 and from 1975 to 1991, respectively. Investigators from these three studies agreed, however, that the presence of residual disease did not affect survival in adults,[18,20,21] a matter of some interest. On the contrary, in the pediatric population, it is a generally accepted criterion that residual tumor of > 1.5 cm² portends a poorer prognosis; however, this cutoff was assigned arbitrarily (R. Packer, personal correspondence). Zeltzer and Packer reported the significance of > 1.5 cm² residual disease only in a subset of patients over 3 years of age with M0 disease, however this was a predetermined criterion for stratification rather than a new finding from this Children's Cancer Group (CCG) 921 phase III trial[12]; both Packer, in a previous study, and the International Society of Paediatric Oncology (SIOP) I trial reported only on extent of resection (EOR) rather than on a specific amount of residual disease.[14,26] and both studies concluded that patients with gross total resections fared better. Whereas in pediatric medulloblastoma, M stage has been consistently associated with prognosis, its importance in adult disease is not as clear. In their study of pediatric medulloblastoma, Evans and colleagues found that 5-year event-free survival (EFS) was 59% for those with M0 compared with 36% for those with M1-3 disease.[8] Kortmann demonstrated a 3-year EFS of 72%, 65%, and 30% for those with M0, M1, and M2/3 disease, although the difference was not statistically significant for M0 and M1.[27] Brandes et al found that stratifying adults with M− (M0) compared with M+ disease (M1-3) resulted in a significant difference in 5-year EFS of 75% vs 45%, and OS of 87% vs 52%, respectively.[18] Despite those findings, however, when Brandes and coauthors reanalyzed their data at a median of 7.6 years, the survival difference between high-risk (T3b-T4, M1-3) and low-risk (T1-T3a, M0) groups was no longer significant, due to late relapses in the low-risk group.[10] At a median follow-up of more than 6 years, a retrospective review of 156 adult patients by Carrie et al also did not find M stage to be prognostic, although only 61% of patients were staged.[21] Similar results were reported in the extension of that study led by Padovani on 246 patients, with a median follow-up of 7 years.[11]

In the era of integrated genomic analyses, specific molecular features appear to provide more reliable prognostic information that reflects their molecular heterogeneity. In general, Group 3 and 4 patients have a worse outcome.[23,24] Compared with pediatric medulloblastoma, MYC/MYCN gene amplifications are rare in adult disease, and chromosome 6 aberrations do not carry prognostic value.[28] In addition to subtype, cytogenetic abnormalities, including loss of 10q, loss of 17p, and gain of 17q, are all associated with poor prognosis and outcome; this is driven in part by the linkage of these abnormalities with SHH pathway tumors, in which they demonstrate prognostic significance. However, Group 4 patients have a worse prognosis, and in this subtype these three cytogenetic changes do not provide additional prognostic information.[24,28] Thus, combining DNA copy number and molecular subtype analyses could provide a robust method of risk stratification. These molecular analyses provide robust information, as they incorporate large numbers of tumors from multiple institutions, allowing for the correlation of subtype and molecular features with outcome. Ultimately, a combination of clinical, histologic, and molecular features might provide a highly reliable molecular/clinical predictor for clinical trial stratification and prognostication.

**Treatment**

**Radiation**

In Cushing’s reported series, the one patient who survived more than 5 years, despite subtotal resection of his tumor, received radiation therapy. Patients who were not treated with radiation postoperatively had an average survival time of less than 6 months.[29] In the ensuing two decades, postoperative posterior fossa radiation gained popularity, although with mixed results due to what we now know to be inadequate dosing and frequent exclusion of spinal radiation, despite Bailey’s findings of frequent spinal subarachnoid tumor seeding in 1930.[30] In their case series published in 1948, Ingraham and colleagues stressed the importance of considering craniospinal radiation therapy (CSRT); however, this therapy was not specified in the report.[31] Five years later, in a landmark paper, Paterson and Farr reported that 65% of patients receiving 50 Gy to the posterior fossa and 35 Gy to the remaining craniospinal axis had a 3-year survival time.[32] Standard-dose
radiation, as supported in the pediatric medulloblastoma literature, is 36 Gy in 20 fractions to the neuroaxis, with an additional boost to the posterior fossa up to a total of 54 to 55.8 Gy.[33,34] A dose of 36 Gy was chosen as the maximal tolerable dose and not based on any other factors. The French Society of Pediatric Oncology (SFOP) M-SFOP 98 protocol randomized patients with standard-risk medulloblastoma to standard vs hyperfractionated radiation to the neuroaxis (36 Gy in 36 fractions), and a posterior fossa boost, with conformal therapy restricted to the tumor bed and to a dose of 68 Gy given in 68 fractions. The 3-year PFS and OS were 81% and 89%, respectively, and chemotherapy was not utilized.[35]

When standard-dose neuroaxis radiation was compared with a reduced dose of 23.4 Gy, this translated into decreased PFS and OS.[36] Since then, other studies have shown that average-risk pediatric medulloblastoma can be treated with decreased doses of CSRT (23.4 Gy) and a focused boost to the tumor bed rather than the entire posterior fossa, with similar results as long as chemotherapy is utilized.[37-39] In univariate analysis of prognostic factors in adult patients with medulloblastoma, both radiation doses to the neuroaxis and the posterior fossa were significant, although only doses to the posterior fossa retained significance on multivariate analysis. Doses to the posterior fossa of less than 50 Gy resulted in inferior outcomes in Padovani’s review of 253 adult patients.[11] Craniospinal irradiation (CSI) is associated with an increased risk of secondary malignancies, endocrine dysfunction, hearing loss, infertility, cardiac disease, and neuropsychiatric disturbances. Furthermore, approximately 40% of adult bone marrow resides in the vertebrae; therefore, myelosuppression can potentially limit therapy.[40]

Based on the theory that decreasing the radiation dose to nontarget organs will mitigate such adverse effects, proton therapy is being used and investigated in some centers. Howell reported on the largest series of medulloblastoma patients between the ages of 2 and 16 years for whom treatment plans utilizing both protons and traditional photon therapy were compared. Twenty of 24 parameters (4 measured each in the esophagus, heart, liver, thyroid, and kidneys) revealed significantly lower radiation doses using proton CSI. Furthermore, proton CSI provided more homogenous target coverage.[41] What remains to be investigated is if this will translate into fewer adverse effects or improved outcomes due to the ability of adults to tolerate chemotherapy.

Chemotherapy

In the 1980s and 1990s, it became widely accepted to use chemotherapy for high-risk pediatric medulloblastoma. Variations among studies in defining those at high risk, and inconsistent staging of the neuroaxis, have made it difficult to generalize the indications for chemotherapy. The SIOP I trial, which closed in 1979, initially reported an overall benefit from chemotherapy in all medulloblastoma patients; however, in extended follow-up, this benefit persisted only among those with residual disease, brainstem involvement, and stage T3-4 disease.[26] In 1990, Evans et al showed that while for the majority of patients with standard-risk disease, the addition of chemotherapy with CCNU (lomustine) and vincristine to RT did not result in a significant benefit, patients in the CCG/RTOG study with T3-4, M1-3 disease who received chemotherapy had a PFS of 46%, compared with a PFS of 0% in those who received RT alone.[8] The report by Zeltzer et al on the CCG phase III study comparing 8-in-1 chemotherapy (cisplatin, cytarabine, dacarbazine, hydrea, lomustine, methylprednisolone, procarbazine, vincristine) against chemotherapy with vincristine, lomustine, and prednisone found the latter regimen to be superior in patients with high-risk disease.[12] As discussed earlier, chemotherapy has been encouraged in pediatric average-risk medulloblastoma, to allow administration of decreased doses of radiation. Packer and colleagues found use of lomustine, cisplatin, and vincristine vs cyclophosphamide, cisplatin, and vincristine to be equally efficacious when given with 23.4 Gy CSRT and 55.8 Gy of posterior fossa RT for average-risk disease in patients between the ages of 3 and 21 years.[42] In 1993, Carrie and colleagues reported on a series of 30 adult patients treated at the Regional Cancer Institute in Lyon. A total of 6 patients did not receive chemotherapy; 7 received lomustine and vincristine after RT; 1 was given a CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen; and 16 were given an 8-in-1 regimen prior to RT, with 10 of the 16 also receiving methotrexate. After the publication of the French M7 protocol, methotrexate was no longer used.[43] These 30 patients were incorporated into a larger retrospective analysis by Carrie and colleagues, published in 1994. A total of 79 of 156 patients treated at 13 French institutions were given RT alone, and two patients did not receive any postoperative therapy. The remaining 75 patients received chemotherapy in addition to RT: 31 were given the 8-in-1 regimen; 29 were given lomustine and vincristine; 9 were given ifosfamide, cisplatin and vincristine; and another 6 patients were given other regimens. No statistically significant differences in outcome were noted among all groups.[21] Prados reported on a series of 47 patients
16 years of age and older. Thirty-two patients had nitrosourea-based chemotherapy, which was correlated with improved survival (P = .03); however, 13 did not have CSF cytology, 34 did not have MRIs, and RT doses varied.[44]

Brandes reported on the only prospective clinical trial for adult medulloblastoma to date, in 2003.[18] Patients with T1-T3a, M0 disease and no residual disease were labeled as “low-risk” based on pediatric literature,[18,45] and were given RT alone. All high-risk patients received 2 cycles of chemotherapy prior to RT, which was then followed by further chemotherapy in cases of metastatic disease. Partway through this trial, Galanis et al reported on 17 adult patients with central nervous system (CNS) embryonal tumors who received chemotherapy. The authors noted that treatment with cisplatin resulted in an 84.5% response rate; this correlated with an increased time to progression compared with nitrosourea therapy, which resulted in a 63.5% response rate.[46]

Prior to Galanis et al reporting their results, patients were given nitrogen mustard, vincristine, prednisone, and procarbazine; after 1995 the regimen was changed to cisplatin, etoposide, and cyclophosphamide. The 5-year PFS was 76% and 61% in the low-risk and high-risk groups respectively, which was comparable to pediatric survival data. This trial was updated in 2007 and, after a follow-up of about 7 years, the initial differences between groups were lost: 5-year PFS was 80% and 69% in the low-risk and high-risk groups, respectively, while the 5-year OS rates were 80% and 73%, respectively. The authors surmised that late recurrences in low-risk patients might be decreased from chemotherapy[10] and that a long follow-up period is necessary to evaluate the real outcome of these tumors in adults. This trial cohort was expanded to a total of 95 patients (30 low-risk and 65 high-risk) and presented in abstract form at the 2010 meeting of the American Society of Clinical Oncology (ASCO). Among the low-risk and high-risk groups, statistical significance was reached in both PFS and OS. In the low-risk patients, PFS outcomes at 5 and 10 years were 78% and 46%, respectively, and in high-risk patients were 50% and 36%, respectively. OS in the low-risk patients was 92% and 65% at 5 and 10 years, respectively, and in the high-risk patients was 58% and 45%, respectively. M0 patients fared better than those with metastatic disease in terms of survival after 10 years of follow-up (62% vs 29%, P = .04), but residual disease had no impact. No deaths occurred from toxicity of therapy.[45]

Timing of chemotherapy and radiation

Concerns regarding lengthy delays before radiation, namely, that chemotherapy-associated myelotoxicity could prohibit neuroaxis radiation, have spurred investigations regarding the optimal timing of therapy. Zeltzer and colleagues found a reduction in 5-year PFS from 63% to 45% in patients for whom chemotherapy preceded radiation; however, this study utilized the 8-in-1 regimen, which is now accepted to be inefficacious.[12] In a randomized study of pediatric patients with either standard-risk or high-risk medulloblastoma, delay of RT by giving neoadjuvant chemotherapy vs postoperative RT followed by chemotherapy decreased the 3-year PFS from 78% to 65%. Further analysis revealed that detriments associated with giving chemotherapy prior to radiation occurred in those patients with standard-risk disease and those aged 6 to 18 years.[27] This study was not well balanced in terms of the duration of chemotherapy, however, and long-term outcomes have not been updated.

In the only prospective trial for adult medulloblastoma, 36 patients received 54.8 Gy to the posterior fossa and 36 Gy to the neuroaxis, with those at high risk receiving 2 cycles of chemotherapy prior to radiation and continuing with chemotherapy after the completion of RT. Imaging was repeated prior to each cycle of neoadjuvant chemotherapy; however, no patient progressed prior to receiving RT. Furthermore, the median duration of RT for those receiving chemotherapy prior to RT and those not receiving chemotherapy did not differ (at 46.5 days and 45 days, respectively). In contrast, all patients required dose reductions of postradiation chemotherapy.[18]

Recurrent disease

Several therapies have been tested for recurrent medulloblastoma. Agents used include cisplatin- and nitrosourea-based regimens, etoposide (Vepesid), dacarbazine, temozolomide, and bevacizumab (Avastin), since medulloblastoma cell lines express vascular endothelial growth factor (VEGF) as well as VEGF receptor (VEGFR)-1 and VEGFR-2.[47] A review of adult patients with recurrent CNS embryonal tumors treated at the Mayo Clinic compared outcomes for 10 patients (8 with medulloblastoma) who received high-dose chemotherapy (HDC) followed by autologous stem cell transplant (ASCT) with outcomes for 13 patients (11 with medulloblastoma) treated with conventional nitrosourea or cisplatin-based chemotherapy. HDC with ASCT was associated with longer time to progression and OS (0.58 vs 1.25 years and 2.00 vs 3.47 years).[48] Several ongoing
clinical trials allow for the enrollment of adult patients with medulloblastoma. In particular, SHH inhibitors such as vismodegib (Erivedge) and LDE225 (Erismodegib, a Smoothened [Smo] antagonist) are promising treatments for medulloblastoma with SHH pathway activation. However, in animal models as well as in a case report in humans,[49] resistance to SHH inhibition develops rapidly,[49,50] and therefore novel combination therapy trials are being developed.

Discussion and Recommendations

The National Comprehensive Cancer Network (NCCN) Guidelines for adult medulloblastoma version 1.2012 promote maximal safe resection followed by postoperative staging. Patients should have a brain MRI scan with contrast 24 to 72 hours after surgery, and imaging of the neuroaxis followed by CSF analysis, with both performed a minimum of 2 weeks postoperatively. Those designated as “standard risk” include M0 patients and those with < 1.5 cm² residual tumor. Those designated ‘high risk’ are patients not meeting those criteria and those with the large-cell/anaplastic subtype.

The importance of extent of resection has been controversial in adults, as summarized previously and noted in Table 2. Results have varied, likely due to the heterogeneous definitions of residual disease. Furthermore, the specific cutoff of 1.5 cm² has not been demonstrated to be of significance in adults and was arbitrarily set in pediatrics. For these reasons, we would caution against dogmatic adherence to this cutoff for residual disease, although without further prospective data it seems reasonable to consider patients without complete resection at increased risk. A minority of adult medulloblastomas have large-cell or anaplastic histology., Data to support the assertion that this histology denotes increased risk were supported in the Remke study, which found all of these to be of molecular subtype D, which had the poorest prognosis.[23] Although inclusion of molecular subtype analysis is not routinely performed, upcoming clinical trials with molecularly targeted therapy will incorporate medulloblastoma subtype as a stratification factor or will be added as a criterion for inclusion.

Especially since medulloblastoma is a very rare tumor in adults, multidisciplinary consultation should precede therapy. Those deemed to be at high risk for recurrence should receive RT followed by chemotherapy, and those at average risk can be treated with either RT alone or with chemotherapy. Based on Packer’s pediatric trial, for average-risk medulloblastoma a cisplatin-based regimen is recommended by the NCCN, with or without vincristine concurrent with radiation. The combination has only proven efficacious in pediatric disease and may prove too toxic in adults, due to the potential for toxicity with lomustine administered in the adjuvant setting.[42] We would propose that “sandwich” chemotherapy with cisplatin, etoposide, and cyclophosphamide may also be considered for high-risk patients per the expanded phase II study by Brandes,[45] since chemotherapy concurrent with radiotherapy has not been clearly shown to have a role in the treatment of adult medulloblastoma. With a growing body of literature to underscore the genetic dissimilarity between adult and pediatric disease, we cannot generalize that regimens efficacious for either population will be universal. There is renewed optimism about treatment of medulloblastoma, following identification of key tumor pathways driving the disease and the development of drugs that inhibit these pathways. An organized, international effort will be essential for the successful evaluation of these new therapies in prospective studies in the adult population.

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