Cancer and Metastasis Reviews (2019) 38:683–694
https://doi.org/10.1007/s10555-019-09831-3

# Wilms tumor, medulloblastoma, and rhabdomyosarcoma in adult patients: lessons learned from the pediatric experience

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Published online: 3 December 2019


## Abstract

Wilms tumor (or nephroblastoma), rhabdomyosarcoma, and medulloblastoma, common embryonal tumors in children, can occasionally occur in adults, for whom survival is significantly inferior than pediatric patients. Available data on adults with Wilms tumor consist of case or case series reports. Among other factors, the unfamiliarity of adult oncologists and pathologists with nephroblastoma and consequent delays in initiating the appropriate risk-adapted chemotherapy may negatively influence outcomes. The survival decrement in adults with rhabdomyosarcoma has been attributed to the lack of centralized care, the inconsistent use of standard protocol-driven multimodal therapy, and lower chemotherapy tolerance in adult patients. In children with medulloblastoma, evidence from randomized clinical trials has led to risk-tailored therapies tuned on histology, extent of initial disease, and biological features. Such refinements are still missing for adults due to the lack of similar trials and studies that might provide the same or a different understanding regarding patients' individual prognosis, treatment morbidity, and quality of life. Recent experiences have suggested that applying or adjusting pediatric protocols to adult patients with these tumors is feasible and can improve survival. Here, we provide an evaluation of the current evidence for the management of Wilms tumor, rhabdomyosarcoma, and medulloblastoma arising in adults. This review aims to promote the referral of adolescents and adults with pediatric tumors to pediatric centers for inclusion into pediatric protocols, or into protocols and studies specifically designed for that age group with the cooperation between pediatric and adult oncologists.

**Keywords** Wilms tumor · Medulloblastoma · Rhabdomyosarcoma

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## 1 Wilms tumor

### 1.1 Background on available experiences

Wilms tumor (WT), also known as nephroblastoma, is considered to be an embryonal tumor owing to its histological mimicry of stages in nephrogenesis and early age of onset. WT is the most common renal cancer in childhood with an annual incidence of 8–10 per million [1, 2]. The median age at diagnosis is 3–4 years and 90% of cases are diagnosed before the age of 7 years [2]. The exact incidence of WT in adults (≥ 19 years of age) remains unknown, representing less than 1% of all renal tumors in adulthood [3–7]. The current estimate for Europe and the United States does not exceed 0.2 per million per year. A population-based epidemiological study from European Cancer Registries study on cancer patients' survival and care (EUROCARE) project, including data from years 1983–1994 from 67 cancer registries covering a population of 100 million in 22 European countries, showed that the

median age at diagnosis for adult WT patients (defined as > 15 years of age) was 34 years [3]. However, the age range was wide with some patients even aged over 60 years [3]. Clinical and radiographic findings of WT in adults seem to be indistinguishable from more common renal tumors, such as renal cell carcinoma. Consequently, a WT diagnoses is usually made after nephrectomy, thereby removing the possibility of preoperative chemotherapy.

The genetic changes that underpin WT in children involve ~40 cancer genes [8]. Many WT-related genes have pivotal roles in the developing kidney, strengthening the evidence for WT origin in early renal maldevelopment [9]. In addition to classical genetic changes involving WT1, the IGF2 locus, WNT pathway, MYCN, and TP53, additional cancer genes that harbor likely driver mutations in WT have been more recently identified. These genes include epigenetic remodelers (SMARCA4, ARID1A), miRNA processor genes, and the transcription factors SIX1/SIX2 [10, 11].

A wide range of syndromes, congenital anomalies, and constitutional chromosomal aberrations have been associated with an increased risk of WT in children [12]. These syndromes do not seem to be responsible for WT in adulthood, although one case of an adult WT patient with a germline WT1 mutation and another one with hypospadias and cryptorchidism have been described [13, 14]. Another study of adults with WT suggested a potential role for the dysregulation of the Wnt-signaling pathway, as also demonstrated in some pediatric WTs [15]. A further adult WT case showed isochromosome 7q as is sometimes seen in pediatric cases [16]. Thus far, only one adult case has been reported with bilateral synchronous WTs, which typically arise in syndrome cases, in contrast to the 5–7% incidence described in childhood [17].

The paucity of data available in adults makes it impossible to determine whether WTs in adults and children are biologically comparable and thus whether similar tumor entities are occurring in a different age group, as suggested by their morphological similarities.

Typically, WT comprises three histological components: blastemal, epithelial, and stromal [18]. The proportion of these components varies significantly, forming the basis for histological classification of WT, which may correlate with tumor genetics and outcome [18, 19]. There are no histological differences between WTs occurring in children and adults. The diagnosis of a WT is somewhat complex and challenging not only for general pathologists who are usually not familiar with the histopathologic features and variants of WT, but also for pediatric pathologists [20].

WT treatment in children consists of surgery, chemotherapy, and additional radiotherapy for select patients (either to the flank or the whole abdomen depending on locoregional disease extent). The backbone of pediatric chemotherapy regimens is composed of vincristine and actinomycin D for low-risk tumors, with cyclophosphamide, etoposide, doxorubicin, and carboplatin added in the highest-risk group [21, 22]. Irinotecan has been recently reported as an effective drug in children with WT, and its inclusion into upfront treatment high-risk regimens is under evaluation [21]. With the introduction of multimodal treatment, long-term cure rates for children have improved to > 90% [2, 10, 23–25]. Two different strategies for managing children diagnosed with a WT exist. In Europe, the majority of children receive preoperative chemotherapy in line with the Société Internationale d'Oncologie Pédiatrique (SIOP) protocols [22]. By contrast, most children in North America undergo immediate nephrectomy as per the Children's Oncology Group (COG) protocols [23]. The 2-year event-free survival (EFS) and overall survival (OS) rates for all children with WT treated in the large-scale European SIOP-2001 trial were 87% and 93%, respectively, with similar results reported in COG protocols [10, 23, 24]. However, given the fact that both approaches share similar outcomes in children, combined with the scarcity of adult cases treated with pre-nephrectomy chemotherapy, the general recommendation on initial management remains unsettled for adults, and an individual assessment is advised.

WT is known to be a very chemosensitive tumor, and modern clinical trials aim to improve risk stratification to reduce the burden of therapy. Both SIOP and COG use tumor stage and histological subtype to stratify recommended postoperative therapies [10]. SIOP classifies tumors as low-risk (completely necrotic), intermediate-risk (epithelial, stromal, regressive or mixed subtypes, including focal anaplasia), or high-risk (blastemal type and diffuse anaplasia) [18, 19, 22]. The blastemal type can be identified by the percentage of blastema remaining after preoperative chemotherapy [18]. COG characterizes treatment-naive histology as favorable (that is, non-anaplastic) or unfavorable (focal and diffuse anaplasia). Since 2005, COG has included a molecular marker in risk stratification, treating children whose tumors have loss of heterozygosity for 1p and 16q chromosomes with more intensive chemotherapy [26]. Chromosome 1q gain represents an additional biomarker recently validated as a negative prognostic factor [11, 27], and will be soon incorporated into COG risk stratification schemes.

For many years the literature has suggested that the survival for adults with a WT is inferior than that for children [3–5, 7, 17, 28]. However, improved outcomes when adults were correctly diagnosed and timely treated according to pediatric protocols have been reported [6, 29]. In 1982, the National Wilms' Tumor Study Group (NWTSG) reported for the first time on adults with WT: 31 patients (51.7% of cases with advanced stage tumors) with a 3-year OS rate of 24% compared with 74% in childhood patients at that time [28]. In 1990, the second report from the NWTSG showed an important improvement with a 3-year OS rate of 67% in 27 adults (median age: 24 years; advanced stage in 58% of cases) by adopting the multimodal treatment protocols used in children [17]. In 2004, the third report from the NWTSG group

demonstrated a 5-year OS rate of 82.6% in 23 adult patients (median age: 21.9 years; advanced stage in 43%) treated similar to their childhood counterparts according to the NWTSG protocols [29]. This improved outcome is similar to the reported outcome in a cohort of 27 German adult patients (median age: 25.4 years; advanced stage in 70% of cases) treated according to the contemporary SIOP protocol [6]. Results from these reports suggest that many adults with WT, if treated appropriately, are expected to be cured especially if the tumor has not spread and/or is resected completely.

There are multiple factors that might explain the survival decrements in adult WT, including the unfamiliarity of adult oncologists and pathologists with the diagnosis of WT, and thus potential delays in initiating the appropriate risk-adapted therapy, inadequate staging due to low rates of lymph node sampling, and under-utilization of proven adjuvant chemotherapy and radiation. For instance, the false presumption of renal cell carcinoma may stall the planning of adjuvant therapy for WT (which is not always needed in adults with renal cell carcinoma) with subsequent reclassification of up to 15–20% of cases after central pathology review [20]. Distinguishing anaplastic WT, which demands more intensive treatment approaches, from other renal tumors can present a challenge for general pathologists [20]. For that reason, each case is reviewed by a panel of expert pathologists in pediatric WT trials [19].

The usual significant delay of commencing postsurgical therapy in adult patients seems to effect outcome adversely [7, 30, 31]. The pediatric WT treatment protocols advise starting adjuvant chemotherapy within 7–14 days after nephrectomy [22]. The 17 adults with a WT reported by the Italian group started adjuvant therapy at a median of 59 days post-nephrectomy: the 10 patients starting treatment within 30 days of diagnosis had a 5-year EFS of 60% compared with 14.3% for the 7 patients with a delay ≥ 30 days ($p = 0.03$), respectively (their OS was 80% versus 28.6% [$p = 0.05$]) [7]. An analysis from the U.S. National Cancer Database showed that a surgery to radiation therapy interval < 14 days correlated to improve OS in children with non-metastatic WT [31]. While reported only in small cohorts to date, there is also evidence of greater chemotherapy-related toxicity in adults. Adult studies moreover report a higher incidence of advanced stage disease (stage III or IV), in the range of 45–70% compared with pediatric patients where approximately one-third of children are classified as stage III or IV after primary nephrectomy [3, 5–7, 17, 28, 29]. It is a known phenomenon that incidence of anaplasia increases with advancing age of affected children [32].

### 1.2 Treatment recommendations for the management of Wilms tumor in adults

As WT rarely occurs in adults, there are no standard treatments or age-specific protocols. Once the diagnosis is suspected, a timely review by an expert pediatric pathologist is key important in order to avoid delay in starting therapy. Recommended staging investigations include a computed tomography scan of the chest and either a computed tomography or a magnetic resonance imaging (MRI) of the abdomen (to detect lung, liver, or lymph node metastases, to assess the patency of Cava vein). The clinical significance of millimetric lung nodules detectable on CT scan remains controversial in pediatric practice but could presumably represent metastatic (unless proven otherwise by histology) disease in adults. Bone, bone marrow, and central nervous system metastases are extremely rare in pediatric patients [33], and thus there is no evidence to support screening for metastases to these sites in adults.

A small number of reports are available to assess treatment prescription and outcome in adults with WT [5–7, 17, 28, 29]. Most patients were treated with initial nephrectomy followed by stage-adjusted chemotherapy with or without local radiotherapy, which have been gradually adapted according to regimens used in pediatric protocols [5–7, 29]. Only 8 patients have been reported to receive preoperative chemotherapy after biopsy [6, 7]. In general, most patients with histology favoring a stage I diagnosis received vincristine and actinomycin D, those with histology favoring a stage II diagnosis received vincristine/actinomycin D with or without doxorubicine and/or radiotherapy, and those with histology favoring stage III and IV disease primarily received the three-drug regimen plus radiation therapy. Data indicate that "exceptions" were often made, with many patients individually treated more intensively than their stage equivalent pediatric counterparts [5–7, 17, 28, 29]. Vincristine intensity was often decreased in adults as compared with current childhood protocols, as adults frequently developed severe peripheral neurological toxicities [6].

A standardized approach for the management of adult WT based on a consensus of experts in the field of pediatric WT has been proposed with the aim of encouraging uniform treatment protocols [30]. Only non-advanced stage patients with optimal staging and short time interval from nephrectomy to start adjuvant chemotherapy should be eligible for the minimum chemotherapy with vincristine/actinomycin D regimens. The consensus recommendation is to consider adding doxorubicin for patients with stage II tumors, which differs from the standard prescription in children, based on the lower survival rate and the concern of average longer delay from surgery to postoperative treatment observed in adults. In the very rare instances when the diagnosis of WT is anticipated on a biopsy, it is worth giving preoperative chemotherapy as it (1) reduces the risk of intraoperative tumor rupture and (2) the in vivo histological response to chemotherapy can be incorporated into the risk assessment [18]. In the cases of pretreated tumors, it is recommended to adopt the SIOP histologic risk classification scheme and nomenclature for reporting [18, 19]. In particular, the recommendation is to treat cases

with blastemal-type histology after pre-nephrectomy chemotherapy as high-risk pediatric cases (i.e., by using etoposide, carboplatin, cyclophosphamide, and doxorubicin plus radiotherapy). There is also a consensus on treating any pattern of anaplasia (that is either diffuse or focal) [32] as high-risk tumors, by using all the effective drugs as combined in more frequently adopted pediatric high-risk regimens [22, 30].

Total nephrectomy with adequate lymph node sampling is recommended according to adult nephrectomy guidelines for any renal cancer, while radical retroperitoneal lymph node dissection is not regarded as standard practice. We recognize that (open or laparoscopic) partial nephrectomy have become the gold standard for low-volume renal tumors in adults, and this approach is under investigation for larger tumors as well [34]. There is increasing awareness among pediatric surgeons that indications to nephron-sparing surgery could be implemented for unilateral WTs as well [35]. It is important to recognize that children are usually submitted to nephron-sparing surgery following the benefits of neo-adjuvant chemotherapy, which almost never occurs in adults. Like in children, WT in adults might be a target for minimally invasive surgery, provided that patient selection and technical factors are carefully addressed [36, 37]. The authors encourage the inclusion of adults in pediatric protocols, such as the contemporary COG trials where cases up to 30 years are eligible for registration, or the recently initiated SIOP Umbrella protocol [22].

## 2 Rhabdomyosarcoma

### 2.1 Background on available experiences

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents, with an annual incidence of 4 per million for 0–19-year-old individuals and approximately 400 cases each year in Europe [38]. Though it is a tumor typical of pediatric age (with its highest incidence before 6 years of age), it can occur also in adults [39]. However, the incidence of RMS declines with age and is extremely rare in adulthood. Soft tissue sarcomas account for only 1% of all adult malignancies, and RMS comprise 3.3% of all soft tissue sarcomas arising in adulthood [39].

RMS displays high propensity for metastatic spread, but also characteristically exhibits high chemosensitivity [38]. Contemporary pediatric oncology studies reported OS rates over 70% for patients with localized RMS treated with risk-adapted therapies including surgery, radiotherapy, and multi-agent chemotherapy [40, 41]. The improvement in pediatric RMS survival rate achieved over the past few decades is due in part to the centralization of care in specialized centers, leading to a wider collaboration on national and international levels and a higher number of cases included in multi-institutional clinical trials. A recent study from the European pediatric Soft Tissue Sarcoma Study Group (EpSSG, which is the largest international cooperative group involving more than one hundred centers from 14 different countries) reported that 77% of expected cases in children and 64% in adolescents were registered into EpSSG trials and studies, and that these percentages were even higher in some countries [42].

For children and adolescents, individual outcome depends on multiple prognostic factors with the most important being histological subtype, primary tumor site and size, lymph node involvement, and distant metastasis. We additionally know that patient age may influence survival probability [39, 43, 44]. The EUROCARE-5 study (referring to 2000–2007 period) reported a 66.6% 5-year OS rate among 0–14-year-old patients, as opposed to 39.6% for patients 15–19 and 36.4% for 20–39 years of age [45]. In pediatric protocols, RMS patients are classified into two groups, younger or older than 10 years, respectively, with the latest group expected to have a less good predicted outcome [38, 43, 44].

Published reports show that adult patients with RMS have a worse prognosis than children. A retrospective analysis reported an OS rate of 21% in adults with embryonal and alveolar RMS [46]. The corresponding 5-year OS for pediatric cases (both embryonal and alveolar) in contemporary international cooperative protocols is in the 70–80% range [38, 40, 41]. Notably the outcome is particularly dismal for young adults (> 19 years) with RMS, as opposed to adolescents (≤ 19 years). The few published series report young adult survival rates in the 20–40% range [39, 46–54]. A study from Surveillance, Epidemiology and End Results database compared the clinical features and outcome of 1071 adults (age > 19 years) with 1529 children and adolescents (≤ 19 years) and found that adults were more likely to present with adverse prognostic variables (aggressive histotypes, unfavorable anatomical sites, and advanced disease at onset more frequently seen) [39]. This study further confirmed a far worse prognosis for adult RMS (5-year OS of 26.6% versus 60.5% in children), regardless of whether variables known to influence survival were present [39]. Embryonal and alveolar RMS (ARMS) were moreover found to display aggressive behavior in adults, excluding the so-called pleomorphic RMS (that should be seen as a pleomorphic sarcoma with myogenic rhabdomyoblastic differentiation and is a specific entity closer to adult non-RMS soft tissue sarcomas than to RMS) [55].

The reason for poor survival in adults is likely to be multifactorial [56, 57]. On one hand, tumor biology may play a critical role in prognosis (e.g., higher intrinsic aggressiveness of RMS arising in older people). In adults, ARMS is associated with a poorer prognosis much more frequently than it is in children. The higher proportion of metastatic adult patients is undoubtedly another factor. Unlike RMS in children, the site of tumor origin has not been reported to be a prognostic factor in adult patients [47–50]. On the other hand, age-related differences in survival might be related to differences in the

clinical management. Adolescents and young adults (AYA) generally achieve the tumor diagnosis after remarkable delay, which may potentially influence a higher tumor stage distribution at diagnosis [58].

Other explanations for this observed survival gap may be the lack of referral to expert centers and inclusion in clinical trials [56, 59], as well as the quality of delivered treatments [50, 54]. In 2003, the authors reported on a retrospective single-center analysis on 171 adults (aged ≥ 18 years) who were treated for RMS between 1975 and 2001 [50]. These data confirmed a less favorable clinical presentation of RMS in adults compared with children (50% of cases had the alveolar type, 60% had tumor arising in unfavorable sites, 32% had regional nodal involvement, and 73% had tumor diameter > 5 cm) in addition to a worse prognosis (5-year EFS rate of 27.9%, OS rate of 39.6%). Importantly, this study meticulously analyzed individual treatments and patients were stratified according to the degree to which they had been treated appropriately based on current treatment guidelines for childhood RMS. Though these adult patients had been treated in a sarcoma-referral center such as the Istituto Nazionale Tumori in Milan, only 39% of them had received a multimodal treatment strategy similar to that applied in childhood RMS that consists of chemotherapy (either cyclophosphamide or ifosfamide and anthracyclines and/or actinomycin-D lasted at least 8 total cycles), surgery, and/or radiotherapy [50]. Overall, it was judged that more than half of the cases had received a potentially inadequate treatment, either because the drugs they received were different from those used in pediatric RMS protocols or because patients were given none or less than 8 courses of chemotherapy (both of which are standard practices in clinical management of adult sarcomas). However, the outcome of adult patients of the Milan series was better for those treated with the pediatric therapeutic approach (OS rate 61% versus 36%) [50].

Since that publication, our institute has adopted various measures to improve the quality of treatment for adult patients with RMS, by increasing the cooperation and managing all adult cases on the strength of a multidisciplinary discussion attended by both pediatric and adult medical and radiation oncologists, developing ad hoc recommendations for the treatment of adult RMS (based on the principles adopted by pediatric protocols), and prospectively registering all adult RMS cases in an institutional database. In 2019, a prospective series of 95 patients (aged 18–77 years) treated from 2002 to 2015 for embryonal and alveolar RMS was reported [54]. The 5-year OS rate of 40.3% of this series might have been influenced by the fact that one third of the cases were metastatic at diagnosis (further confirming the prevalence of aggressive features in adult RMS). However, improving specific recommendations enabled us to increase the number of patients receiving an intensive multimodal treatment resembling the pediatric treatment strategy by up to 70% (versus 39% in the retrospective series). Adults treated with pediatric-like protocols displayed improved outcome: patients with localized disease (whose OS rate was globally 51.8%) had an OS rate of 58.8% if scored 1 (i.e., treated as children) versus 30.3% if scored < 1. This data reinforced the assumption that adherence to the principles of pediatric protocols may add improving outcomes in adult RMS. Important to note, one main conclusion from that study was also that treating adults with pediatric-type strategy was not enough to replicate the results observed in children. An additional major issue concerned treatment compliance: 30% of patients did not receive the whole treatment compliant with pediatric principles, mainly due to chemotherapy-related toxicity (in 44% of cases the scheduled chemotherapy was adjusted, and in 57% of cases delays in the treatment administration were recorded) [54]. These findings support that adults may display a reduced tolerance to intensive treatments originally designed for children (e.g., they experience more vincristine-related neurotoxicity and likely more hematological toxicity) [60, 61].

## 2.2 Comments on treatment

Broader cooperation between pediatric and adult oncology groups is needed to improve the quality of care given to adults with RMS. We may consider to raising the upper age limits in pediatric RMS cooperative protocols (as was recently done in some international trials) to allow inclusion of adults. To this purpose, we recommend that adult teams be included in the development of these protocols as physicians may otherwise be reluctant to enroll patients into trials in which they themselves have no role. Since the compliance and treatment tolerance in adults might be a challenge, the development of international protocols dedicated to adults with RMS should consider a more appropriate use of standard therapies. Recently published results of the EpSSG RMS 2005 protocol in pediatric patients showed that the addition of 6 months of maintenance chemotherapy improved OS for high-risk pediatric localized RMS patients who achieved a complete response to induction therapy [41]. COG pediatric RMS protocols already have more prolonged treatment schedules [40]. It would therefore be worthwhile to consider prolonged or maintenance chemotherapy regimens in adult patients with demonstrated chemosensitive tumors. These concerns highlight the need for novel therapeutic drugs/strategies specifically designed for adult patients. However, identifying new RMS-specific molecular targets for therapy re-direction and development requires gaining a better understanding of the biology of the disease and the different molecular profiles of adult and pediatric RMS cases.

We cannot exclude that part of the prognostic gap between children and adults is attributable to biological differences in RMS arising at different ages. While our knowledge about the complex genomic landscape of pediatric RMS is constantly

increasing [38], there is still a shortage of information (and a lack of ongoing studies) on the biology of RMS in adults. Understanding the tumor biology that differentiates pediatric from adult RMS may provide critical information to drive new initiatives to improve outcomes. Researchers from our group recently reported on a study on microRNA (miRNA) and gene expression profiling on a cohort of 49 RMS cases, 28 children (0–14 years old), and 21 AYA (15–35 years old) [62]. The miRNA analysis identified miR-223 overexpression and miR-431 downregulated in AYA. The correlation with gene expression profiling data further showed that miR-223 was associated with the up-regulation of epithelial–mesenchymal transition and inflammatory pathways, while miR-431 expression correlated to myogenic differentiation and muscle metabolism. In addition, gene expression profiling showed an increase in genes associated with CD4 memory resting cells and a decrease in genes associated with T-cells in AYA RMS. Immunohistochemistry analysis demonstrated an increase of infiltrated CD4, CD8, and neutrophils in AYA RMS tumors. These results showed that aggressiveness of AYA RMS could be partially explained by differences in microenvironmental signal modulation mediated by tumor cells, suggesting a fundamental role of immune contexture in AYA RMS development [62]. While further investigations are needed, this study demonstrates that a better knowledge of biological mechanisms behind RMS pathogenesis in relation to patients' age might be critical to improving the clinical management of adults with RMS.

## 3 Medulloblastoma

### 3.1 Background

Medulloblastoma (MB) comprises a biologically heterogeneous group of embryonal tumors of the cerebellum and is the most common type of brain tumor in childhood [63–66]. Its annual incidence in pediatric age is 6.5 cases per million. By contrast, MB is very rare in adults, accounting for less than 1% of intracranial tumors, with an annual incidence of 0.6 per million [63, 67, 68]. The median age of MB diagnosis in adults is around 30 years old with very few cases diagnosed above the age of 40 years [69]. Endocranial hypertension and associated cerebellar syndrome are the primarily manifesting symptoms of MB. Brain MRI performed before and within 48 h after surgery, spinal MRI (preferably before surgery), and CSF cytology (ideally > 15 days following surgery due to post-operative risk of false–positive results) are key to classify patients according to Chang staging system [70] (namely, M0 stage: no metastasis; M1: tumor cells in the CSF; M2: nodules in the cerebellum, cerebral subarachnoid space, or fourth ventricle; M3: nodular diffusion to the spinal subarachnoid space; and M4: metastases outside the CNS). In both pediatric and adult patients, MB is an aggressive tumor and with a tendency to metastasize throughout the central nervous system via the cerebrospinal fluid (CSF) in up to 40% of cases. Current treatments achieve 5-year OS and EFS rates of up to 85.9% and 82.6%, respectively, for children with average-risk (called standard-risk in Europe) MB [71].

In addition to the histological subtypes of MB (classic, desmoplastic/nodular, large cell/anaplastic, and extensive nodularity), the discovery of distinct molecular subgroups has greatly improved our understanding of the molecular drivers of MB and is being incorporated into prospective clinical trials in pediatric MB [65]. The four major molecular types are SHH, WNT, group 3, and group 4. These main subgroups have been also further divided into 12 subtypes based on distinct somatic copy-number aberrations, activated pathways, and clinical outcomes [72], which describe the unexplained variations seen in clinical behavior and response to therapy in the 4 subgroups.

MB in adults differs biologically from its pediatric counterpart [66, 73]. The majority of cases of adult MB (about 50–60%) are classified as classic or desmoplastic and belong to the SHH subgroup. They mainly involve mutations implicating a loss of function in PTCH1, with some TP53 mutations, due to an underlying germ mutation in 50% of cases. The presence of PTCH1 and SMO gene mutations distinguish adult SHH-type MB from SHH pediatric MB. The prognosis is intermediate, with a 5-year OS of 70% in patients without p53 mutation [73]. Group 4 and WNT account for 25% and 10–15% of adult MB, with 5-year OS rates of 47% and > 80%, respectively, in adults [73–75]. Adult WNT tumors are sporadic, though there may be an underlying Turcot syndrome (patients are predisposed to MB due to a constitutional APC gene mutation), their histological subtype is typically classic and rarely metastasize [73]. The main genetic alterations seen in group 4 adult MBL are MYCN and CDK6 amplifications. In contrast with pediatric MB (in which group 3 represents 28% of all cases), this subgroup is extremely rare in adulthood (< 2%), and has a strong tendency to metastasize (reported in 45% of cases) [73]. The most frequent mutation/amplification is the proto-oncogene MYC. As in pediatric MB, two clinical risk classes are identified in adults based on stage and extent of residual disease after surgery, though the latter factor is highly controversial and its prognostic value in adults has not been validated [74]. There is a consensus to classify adults into either high-risk (presence of metastases [M1-M2-M3-M4 according to Chang] and/or residual disease after surgery) or standard-risk (all the remaining patients) categories.

Management of adult MB is largely inferred from pediatric trials as prospective studies in adults are scarce due to the rarity of the disease in adults. Despite this, large retrospective studies have been instrumental in providing rationale for modern treatment recommendations [69, 75, 76]. Current conventional management of adult MB includes maximal safe

resection followed by craniospinal radiation with or without concurrent and/or adjuvant chemotherapy, depending on clinical risk stratification [64, 65]. Given a perceived (but poorly studied) higher tolerance of radiotherapy in adults compared with children, and poorer tolerance of chemotherapy in adults, until recently chemotherapy was generally reserved for adults with high-risk disease although with high variability of care within and among different institutions. In addition, the benefit of chemotherapy in M0 patients who had received high dose craniospinal irradiation was uncertain. A common practice for the last several decades has been to treat patients with complete resection and non-metastatic dissemination with craniospinal irradiation alone, whereas patients with incomplete resections and/or metastatic dissemination were treated also with upfront chemotherapy [77]. However, this approach has raised important criticisms. Firstly, the clinical risk stratification on which this treatment decisions are based is extrapolated from pediatric experience yet not sufficiently validated in adults. Two recent large retrospective studies (a National Cancer Data Base analysis and a meta-analysis) [69, 78] and two prospective protocols [77, 79–81] have provided evidence supporting the use of upfront chemotherapy and demonstrated its feasibility in adult MB patients, including those with standard-risk or non-metastatic disease, which represent the majority of patients. Long-term surveillance is indicated in adult MB patients as late recurrences are common (median time to first recurrence was of ~ 8 years in our unpublished case series).

### 3.2 Available data on current treatments and possible therapeutic recommendations

Conventional radiation treatment consists of craniospinal irradiation at a total dose of 36 Gy, with a boost of 18–19.8 Gy to the posterior fossa (up to a total dose of 54–55.8 Gy), in fractions of 1.8 Gy each. It is recommended that craniospinal irradiation should be performed by experienced teams and at centers that treat pediatric patients, in order to avoid the risk of under- or overdosing given the complexity of the target organ and the need for field junctions with a meticulous setup. From a technical standpoint, intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and helical tomotherapy (TOMO) have recently been developed for craniospinal irradiation. These methods are both better able to cover the target volume and to spare the organs at risk. The limited availability and high cost of proton technology are currently the obstacles to its use in adults.

Current available data supports the use of adjuvant chemotherapy in adults with standard-risk MB. In these patients, standard-dose craniospinal irradiation followed by chemotherapy (lomustine, cisplatin, and vincristine) achieves 4-year EFS and OS rates of 68% and 89%, respectively [82]. Adult patients' tolerance of chemotherapy following radiotherapy is generally lower and these treatments should therefore be applied at centers that specialize in neuro-oncology. In an Italian series of 43 standard-risk adult MB patients, chemotherapy with DEC regimen (cisplatin, etoposide, and cyclophosphamide) was added to radiotherapy in 15 cases, reaching a 10-year OS rate of 100% as compared with 79% for those treated with irradiation alone [83]. According to the authors, the DEC regimen seemed more feasible for adults than the pediatric regimens.

Two large retrospective studies have demonstrated the benefit of upfront chemotherapy in standard-risk adult MB patients [69, 78]. A large study from the U.S. National Cancer Data Base reported on 751 adults (median age 29 years; range 18–85 years, 88% with M0 disease), who were diagnosed with MB between 2004 and 2012 and received adjuvant craniospinal irradiation plus chemotherapy (69%), or irradiation alone (31%) [69]. This national database analysis demonstrated that combined postoperative chemotherapy and radiotherapy were associated with superior survival for adult MB compared with radiotherapy alone (5-year OS of 86% versus 72%), even for M0 patients who receive high-dose craniospinal irradiation. Kocakaya et al. showed in a meta-analysis of the role of chemotherapy in adult MBL that adjuvant chemotherapy improved survival of adult MB patients (20% of whom showed signs of metastases) [78]. In an international retrospective study on 206 adults (median age 29 years; range 16–66 years; 62% with M0 disease) diagnosed between 1976 and 2014 and registered within the Rare Cancer Network, patients given chemotherapy (48% of the cohort) also had a better local disease control and longer survival [68].

Importantly, combining chemotherapy (usually with platinum-containing regimens) with better staging and patient selection could enable adults with standard-risk MB to benefit from lower doses of craniospinal radiation, as reported in childhood [64, 65]. A French study on 253 adults (124 at standard-risk) showed no survival differences between patients treated with craniospinal irradiation doses > 34 Gy and those given < 34 Gy plus chemotherapy [84]. This finding is supported by an American study on 29 adults, including 7/17 standard-risk patients given craniospinal irradiation reduced doses of 23.4 Gy with concurrent and adjuvant chemotherapy; remarkably, none of these patients relapsed [85]. A subgroup of 9 standard-risk adult patients treated with craniospinal irradiation reduced-dose 23.4 Gy plus chemotherapy according to the German HIT 2000 study displayed the same prognosis as 47 patients treated with craniospinal irradiation alone at doses of 35.2 Gy [82].

Reducing the dose of craniospinal irradiation for adults is likely to favorably impact patients' neurocognitive outcome and quality of life [67, 86]. For children with standard-risk MB, it has recently been established that 23.4 Gy represents the lower threshold dose of craniospinal radiation (if combined with chemotherapy), below which it is not prudent to

go, except in extremely selected conditions [64, 65]. We neither know the threshold dose for adults nor whether it might differ from that of pediatric MBL with the same histology and biological characteristics. In modern pediatric protocols, the possibility of delivering the radiotherapy boost to the tumor bed alone, instead of the whole posterior fossa, is under consideration, achieving a significant reduction in the dose to the supratentorial lobes, cochlea, and hypothalamus, yet this does not represent a standard recommendation to transfer to adults as well. Additionally, the feasibility of applying pediatric protocols for use in adults is sometimes hampered by hematologic and neurological toxicity. In a recent phase II study of radiochemotherapy for adult with MB (which treated 30 patients aged > 21 years with craniospinal radiation and concurrent vincristine followed by cisplatin, lomustine, and vincristine), 70% of patients received more than 4 cycles of this regimen, but all needed dose reduction [81].

The European SIOP PNET-5 randomized trial (which is still underway since 2014) is open for registering young adults up to 22 years of age. Patients are stratified according to a set of clinical parameters (as outlined above), pathological (absence or presence of anaplasia), and biological criteria (C-MYC and MYCN amplification, nuclear expression, and mutation for beta-catenin). For patients with a more favorable prognostic profile, a lower dose of craniospinal radiation and a total number of chemotherapy courses are delivered. Candidates for this less intensive approach are identified based on the abovementioned standard-risk criteria plus nuclear beta-catenin expression confirmed by at least another analytical method (mutation analysis with the FISH technique or cytogenetic analysis of chromosome 6 deletion). The remaining standard-risk patients are randomized to one of the two groups, one of which is given daily carboplatin concomitant to radiotherapy, then subsequent chemotherapy is the same for the two groups, for a total of 8 courses (https://clinicaltrials.gov/ct2/show/study/NCT02066220).

High-risk MB demands treatment with both radiotherapy and chemotherapy, though the sequence and doses involved remain controversial [67, 76]. The long-term survival of high-risk MB patients of any age is still < 70% [87, 88]. Within the SIOP group, there is the intent to examine in children the effect of combined chemotherapy and radiotherapy in a randomized fashion, by comparing different doses and fractions of craniospinal radiation, myeloablative versus conventional doses of chemotherapy, and to explore the value of adding maintenance chemotherapy.

With prolonged follow-up, adults with MB have a worse prognosis than pediatric patients. They should therefore be followed up for a lengthy period of time also because of their long-term sequelae in at least 60–70% of cases (hormonal and/or neurocognitive deficits, and/or second tumors if exposed to nitrosoureas, alkylators, or etoposide) that deserve access to multi-specialist advice for endocrine, cognitive, and neurological issues. The high incidence of infertility in the face of the high duration of life makes it necessary to propose the cryopreservation of their gametes.

## 4 Concluding remarks and perspectives

Optimal management and access to care remain a challenge for many adults with RMS, WT, and MB, which translate into worse outcomes when compared with children [89]. While older patients are more likely to have competing health risks to death (see cardiac or metabolic diseases), age alone is unlikely to be the sole driving factor for this survival difference. A standardized model of care for adults who develop pediatric tumors (or for children and adolescents who have tumors typical of adulthood) has yet to be established, as neither the pediatric nor the adult oncology systems seamlessly fit the needs of such patients [57, 90].

A discussion on potential reasons for adult embryonal tumors experiencing a worse survival, as presented in this review, is instrumental to identify areas for potential improvement, since some of these factors are modifiable. Historically, pediatric oncologists have focused on channeling patients in a limited number of reference centers to guarantee the highest standards of care, and to include as many cases as possible into clinically controlled protocols. Most pediatric clinical trials are designed to tailor the intensity and complexity of therapies on the individual risk of failure, to minimize acute and late toxicities without jeopardizing survival rates [91]. Undertreatment, under-staging, poor compliance with the golden standard therapeutic guidelines, low registration rate into trials, and lack of centralized review of histological diagnosis represent critical issues in adults with rare pediatric tumors. Overall, the rate of participation into clinical trials among 20- to 29-year-old young adults is less than 2% [42, 59, 90].

The use of pediatric protocols for patients of all ages with cancers typical of developmental age has been shown to produce better outcomes for various malignancies [6, 17, 29, 53, 82, 92], and to extend age cutoff for inclusion up to adulthood for some pediatric protocols could be pursued [22]. On the other hand, there is evidence for higher incidence of acute toxicity, leading to lower compliance to protocol prescribed therapy intensity, when pediatric protocols are administered in adults, and this may negatively impact on final outcomes [60, 61, 81]. For daily clinical practice, closer collaborations between adult and pediatric oncologists may increase mutual knowledge of the disease and treatment tolerability, improve care and awareness of available trials with upper age limits beyond pediatric age.

To further advance outcomes in adults, improved age-specific risk classification schemes are needed to better direct therapy beyond the limitations of current stratification based on age, histology, and staging of tumor (these last two factors

being adopted from pediatric studies). Most of our knowledge on the genetics, molecular biology, treatments, and prognosis of embryonal tumors derives from studies done in children. Thus, novel studies focused on better characterizing the same features in adult tumors, as well as extensive efforts at bridging pediatric and adult oncologists and their respective practices, is necessary to move closer to treating these devastating malignancies in adults.

**Acknowledgments** We thank Associazione Bianca Garavaglia Onlus for their constant support.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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