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REVIEW ARTICLE

Medulloblastoma and central nervous system germ cell tumors in adults: is pediatric experience applicable?

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Abstract

Medulloblastoma and central nervous system (CNS) germ cell tumors are very rare in adults, while they account for 25% and 5% of brain tumors in children, respectively (Pastore et al. Eur J Cancer 42:2064–208, 2006). Pediatric experiences, mostly from randomized and controlled clinical trials, have led to different tailored treatments, based on various risk factors, including histology, and extent of disease. For medulloblastoma, biological features have recently emerged that enable therapies to be scaled down in some cases, or pursued more aggressively in the event of chromosomal and/or genetic alterations (Massimino et al. Crit Rev Oncol Hematol 105:35–51, 2016). Such refinements are still impossible for adult patients due to the lack of similar clinical trials that might provide the same or a different understanding regarding patients' prognosis, long-term survival, quality of life, and acute and late toxicities. This review aims to contribute to the debate on the treatment of adults with these two diseases and promote the creation of broad-based, national and international trials to advance our knowledge in this area and to share the skills between pediatric and adult oncologists as adolescent and young adults (AYA) brain tumor national boards are currently requiring.

Keywords Medulloblastoma · CNS germ cell tumors · Adults · Childhood cancers

Introduction

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 [1].

Historically, pediatric oncologists have focused on concentrating patients at a limited number of referral centers to achieve the highest standards of care. Most clinical trials on pediatric cancers are in phase III (randomized or risk-based) and are designed mainly to adjust the intensity and complexity of therapies to reduce acute and late toxicities and without impairing survival rates [2, 3]. 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 [4, 5]. Of course, it is always hard to say whether a given type of cancer would have a different clinical behavior and biological pattern when it occurs in adults as opposed to children.

Medulloblastomas and CNS germ cell tumors are typically of pediatric histologies. They are sensitive to both radiotherapy and chemotherapy and potentially curable. Current treatments achieve 5-year overall survival (OS) and event-free survival (EFS) rates of up to 85.9% and 82.6%, respectively, for children with "average risk" ("standard risk" in Europe) medulloblastoma [6]. Such favorable outcomes are essential, thanks to clinical protocols implemented as a fundamental part of cancer research that benefit both the scientific community and successive generations of patients. Cooperative clinical trials, preferably adopting a randomized design, are the best way to compare the efficacy of new treatments with that of

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standard options. The situation is different for adults: the rate of participation in clinical trials among 20- to 29-year-olds is less than 2% [7].

Here we describe the treatment behavior of two typical pediatric tumors that occasionally occur in adults, i.e., medulloblastoma and germ cell tumors of the central nervous system.

Medulloblastoma

Medulloblastoma (MB) is an embryonal tumor that originates in the posterior cranial fossa, tending in up to 40% of cases to spread via the cerebrospinal fluid (CSF) throughout the central nervous system (CNS). Its incidence in pediatric age is 6.5 cases per million, while in the Italian adult population, it is just 0.5 cases per million [8]. The median age of adult patients with MB is about 30 years, with very few cases over the age of 40 and 25% of patients diagnosed between 15 and 44 years. The male-to-female ratio is approximately 3:2 [9–11]. It is the most common malignant brain tumor in children (15–25% of all primitive brain tumors), while it accounts for less than 1% of CNS cancers in adults.

MB manifests itself mainly with endocranial hypertension associated with cerebellar syndrome. Brain MRI performed before and within 48 h after surgery, spinal MRI (preferably before surgery), and CSF cytology (ideally 15 days after surgery—not beforehand—because of the risk of obtaining false-positive results) are the key tests used to assign patients a stage M according to Chang [12]. Stage T, which refers to the size of the primitive tumor and its relation to the floor of the fourth ventricle, is no longer of prognostic relevance, so:

M0: no metastasis
M1: cytologically positive CSF
M2: nodules in the cerebellum, cerebral subarachnoid space, or fourth ventricle
M3: nodular diffusion to the spinal subarachnoid space
M4: metastases outside the CNS

In addition to the well-established histological variants (classic, desmoplastic/nodular, with extended nodularity, large cell/anaplastic), at least four molecular groups have been defined in pediatric tumors: WNT, SHH, group 3, and group 4 (the latter two are also known as non-SHH and non-WNT).

MB in adults is an orphan disease that differs biologically from its pediatric counterpart [13]. Activation of the WNT pathway is sporadic (occurring in about 10% of adult cases), though there may be underlying Turcot syndrome (patients are predisposed to MB due to a constitutional APC gene mutation), and the histological subtype is typically classic. Adult WNTs rarely metastasize, and the 5-year survival rate is 80% (lower than that in childhood). The majority of cases of adult MB are classified as classic or desmoplastic and belong instead to the SHH subgroup (about 50–60% of cases). 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 survival of 70% in patients without p53 mutation. Group 3, extremely rare in adulthood (< 2%), has a strong tendency to metastasize (45%). The most frequent mutation/amplification is the proto-oncogene MYC. Finally, 20–25% of adult MBs belong to group 4. They are more likely to affect males. The main genetic alterations are MYCN and CDK6 amplifications. The 5-year OS for localized forms is 75% [13–15].

As in pediatric MB, two clinical risk classes are identified 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.

High risk: presence of metastases (M1-M2-M3-M4) and/or residual disease after surgery
Standard risk: all other patients

Standard-risk patients in Europe: children vs adults

For young MB patients, the European study is underway since 2014—PNET 5, proposed by the International Society of Pediatric Oncology (SIOP), for which adolescents (up to 22 years) are also eligible—and stratifies patients according to a set of clinical parameters (as outlined above), pathological criteria (absence or presence of anaplasia), and, for the first time in the history of this disease, biological factors (C-Myc and MycN amplification, nuclear expression and mutation for beta-catenin) identified on tissue analysis. For patients with a more favorable prognosis, a lower total dose of craniospinal radiotherapy (CSI) and a total number of chemotherapy cycles are delivered. Candidates for this approach are identified based on the abovementioned standard risk criteria plus nuclear beta-catenin expression confirmed by at least one other analytical method (mutation analysis with the FISH technique or cytogenetic analysis of chromosome 6 deletion). Other standard-risk patients are randomized to one of two groups, one of which is given daily carboplatin during radiotherapy, then subsequent chemotherapy is the same for the two groups, for a total of eight cycles (https://clinicaltrials.gov/ct2/show/study/NCT02066220).

Given its rarity, the treatment of adult MB is essentially based on pediatric experiences, or small retrospective adult studies, or data from a few prospective studies on adults [16–19]. Conventional treatment for adults with standard-

risk MB generally consists of surgical resection followed by CSI at a total dose of 36 Gy, with a boost of 18–19.8 Gy to the posterior fossa, for an overall dose 54–55.8 Gy, in fractions of 1.8 Gy each. CSI should be performed by experienced teams, at centers that treat pediatric patients, to avoid the risk of under- or overdosing, given the complexity of the target 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 CSI. These methods are both better able to cover the target 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.

In adult patients, standard-dose CSI followed by maintenance chemotherapy (CCNU, cisplatin-vincristine) achieves 4-year EFS and OS rates of 68% and 89%, respectively, in standard-risk patients [20].

In Italy, 43 average-risk adult MB patients received adjuvant RT from 1988 to 2012. Fifteen (34.9%) patients were also given chemotherapy (DEC regimen: cisplatin, etoposide, cyclophosphamide), administered before, after, or both before and after RT. OS rates at 5, 10, and 15 years were 100%, 100%, and 100%, respectively, in patients treated with RT and chemotherapy, versus 100%, 79%, and 60% in those treated with RT alone. According to the authors, the cisplatinum/etoposide chemotherapy regimen seemed more feasible in adults than the pediatric schemes [21].

In the literature and recent experiences, the pediatric approach has also been applied and encouraged for young adults and adults [22, 23]. In standard-risk patients, overall CSI doses could be reduced if CSI is followed by adjuvant chemotherapy, usually with platinum-containing regimens. Reducing the dose of CSI for adults, as done in children, is likely to favorably impact patients' neurocognitive condition and quality of life [10, 24].

A French study on 253 adults (124 at standard risk) showed no differences in OS between patients treated with CSI doses > 34 Gy and those given < 34 Gy plus chemotherapy [25]. This finding is supported by an American study on 29 adults, including 7/17 standard-risk patients given CSI doses of 23.4 Gy with concurrent and adjuvant chemotherapy: none of these patients relapsed [23].

The German HIT 2000 study found that a group of standard-risk patients (no. 9) treated with CSI "reduced doses" of 23.4 Gy plus chemotherapy had the same prognosis as patients (no. 47) treated with CSI alone at doses of 35.2 Gy [20].

A large retrospective study on 751 adults (median age 29 years; range 18–85, 88% with M0 disease), diagnosed between 2004 and 2012, and extracted from the US National Cancer Data Base, reported on patients that received CSI and some also chemotherapy. The 5-year OS was significantly superior in the group that had received both RT and chemotherapy than in the group only treated with RT (OS at 5 years 86% vs 72%, $P < 0.0001$). Overall, the best survival outcome was for patients staged as M0 given the combined therapy and those treated with CSI doses of 36 Gy. Patients given doses between 30 and 36 Gy CSI appeared to have similar outcomes [26].

Finally, an international retrospective study collected 206 patients (median age 29 years; range 16–66), 62% with M0 disease, diagnosed between 1976 and 2014 and registered with the Rare Cancer Network. Ninety-six percent of patients had received CSI and 48% had also chemotherapy. In a multivariate analysis, patients' Karnofsky Performance Status (KPS-80) was prognostically significant for local control, PFS, and OS ($P < 0.04$). Patients also given chemotherapy had a better local disease control and longer survival [27].

In conclusion, several published analyses highlight the potential role of adjuvant chemotherapy in adults. Adding chemotherapy, combined with better staging and patient selection, could enable adults with standard-risk MB to benefit from lower CSI doses, as seen in pediatric age. The effectiveness of such an approach would ideally need to be demonstrated using non-inferiority studies (Fig. 1). For children with standard-risk MB, it has recently been established that 23.4 Gy is the threshold dose of CSI (combined with chemotherapy) below which it is not prudent to go, except in extremely selected conditions [10]. We neither know the threshold dose for adults nor whether it might differ from that of pediatric age with the same histology and biological characteristics. Similar considerations can also be applied to any boosting, as conventional irradiation of the whole posterior fossa implies irradiating about 35% of the whole brain and 60% of the temporal lobes [28]. In modern pediatric protocols, the possibility of delivering the RT boost to the tumor bed alone, instead of the whole posterior fossa, is considered, achieving a significant reduction in the dose to the supratentorial lobes, cochlea, and hypothalamus.

The feasibility of applying pediatric protocols to adults is sometimes hampered by the toxicity for bone marrow and peripheral nerves. In the near future, different subgroups of MB could be given personalized therapies. In particular, the next EORTC trial (EORTC-1634-BTG) will explore the activity of a SMO inhibitor for patients with SHH-MB, the reduction of CSI dose for SHH and WNT-MB, and the intensification of treatment for prognostically bad biological feature MB. All the diagnostic and therapeutic procedures will be centrally reviewed and neurocognitive outcome will be evaluated.

High-risk patients in Europe: children vs adults

High-risk MB demands treatment with both RT and chemotherapy, though the sequence and doses involved remain controversial [10, 19]. The long-term survival of high-risk MB patients of any age is still less than 70% [29–32]. A coming

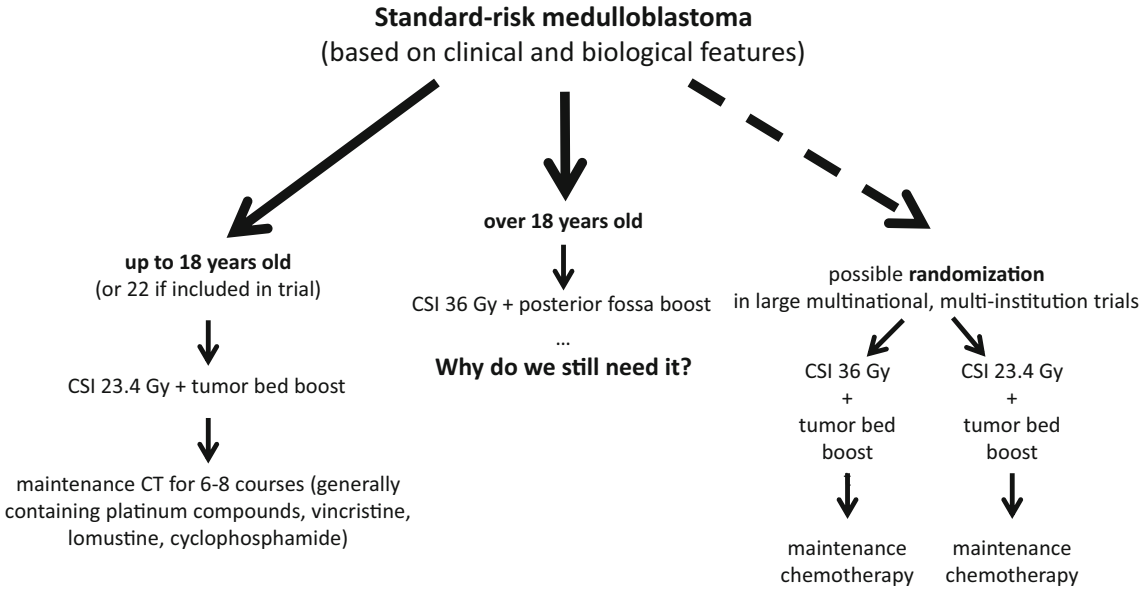

Fig. 1 Standard-risk medulloblastoma therapeutic flow chart in children and adults

study by SIOP will examine combined chemotherapy and RT approaches in a randomized manner. Different doses and fractions of CSI, myeloablative versus standard chemotherapy doses, and the value of "maintenance" chemotherapy will be examined. The results of this very complex controlled study may shed more light on the different therapeutic options used so far, including their value in young adults.

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 [33].

Germ cell tumors

CNS germ cell tumors have an incidence of 0.1 per 100,000 population a year. They are < 1% of all intracranial adult neoplasms and virtually only occur in the second and third decades of life. In fact, 60–70% of cases are diagnosed in patients under 20 years old, about one in two patients are aged between 10 and 19, and only 10% are over 30 [34]. They develop mainly along the midline, in the pineal or suprasellar region. They are histologically divided into pure germinomas, non-germinomas, mixed forms, embryonic carcinoma, yolk sac tumor or endodermal sinus tumor, choriocarcinoma, and immature and mature teratoma. Klinefelter syndrome (47, XXY) is associated with a higher risk of CNS germ cell tumors [34].

In 10% of cases, these neoplasms can be bilateral or, rarely, involve the thalamus. CSF dissemination occurs in 10–20% of cases. A pure germinomatous histology, no CSF dissemination, and no secondary spread detected with spinal MRI represent the main favorable prognostic factors.

Diabetes insipidus, intracranial hypertension, hydrocephalus, and visual disturbances are the main symptoms. Suprasellar tumors are often the cause of multiple endocrinopathies, the most common being diabetes insipidus [35]. The essential diagnostic tests include cerebral and spinal MRI, CSF cytology, and the search for markers (beta-HCG, alpha-FP) in the CSF and serum, chest X-ray, and testicular and pelvic ultrasound.

Alpha-FP levels typically increase in the presence of yolk sac tumor (often more elevated in serum than in CSF), while beta-HCG increases with choriocarcinoma. Lumbar puncture to collect CSF is the gold standard and must be carried out in safe conditions. In the event of severe hydrocephalus, it is advisable to collect CSF during the shunting procedure or third ventriculostomy.

It is important to emphasize that tumor marker assays in the CSF and serum should always be done at the same time, before any other diagnostic investigations, if intracranial germ cell tumor is suspected. According to SIOP, beta-HCG levels > 50 IU/L and alpha-FP > 25 ng/mL in the CSF and/or serum are diagnostic of mixed or non-germinomatous malignant forms. Alpha-FP is never elevated in germinomatous forms, while a slight increase in beta-HCG (< 50 ng/mL) may be observed in 40–60% of cases [36]. Some forms of tumors (the syncytiotrophoblastic variant) can secrete beta-HCG without any increase in alpha-FP [37]. Cases with bifocal

sites, non-secreting, are most likely to be germinomas and do not need a diagnostic biopsy. In the presence of altered markers, treatment can be started without a histological diagnosis, reserving histological confirmation for any surgical "second look" for the removal of post-chemotherapy tumor residues or residual mature teratoma. For proper diagnosis, however, finding normal marker levels suggests the need for a biopsy for histological confirmation. A neuro-endoscopic biopsy is preferable for tumors developing in the third ventricle. It enables sampling of the neoplastic tissue and CSF, and shunts or ventricular catheters for CSF decompression. The 10-year OS for CNS germ cell tumors is > 90% for germinoma and > 75% for mixed forms. Given the particular radio- and chemo-sensitivity of germinoma, surgery is mainly to establish the lesion's histology. Up-front surgery with curative intent has to be excluded for the risk of neurological and endocrinological sequelae without benefit in survival [38]. It is only for well-differentiated (mature) teratomas that surgery as radical as possible has a primary role, affording an excellent long-term disease control, given the radio- and chemo-resistance of these tumors.

Historically, the treatment for pure germinomas consisted of a stereotactic biopsy followed by CSI (30–36 Gy), with a boost of 14 Gy to the primary lesion (overall dose 45–50 Gy) [39]. CSI assures excellent long-term disease control in all patients with germinomas, regardless of disease stage and completeness of the diagnostic process [40].

There is no evidence to suggest that the treatment provided in pediatric age produces different results in adult cases (although the data are limited) [41–43]. The potential long-term toxicity of CSI, especially in younger patients, has prompted efforts to reduce the volume and dose of RT, with or without associated chemotherapy [44]. The dose currently considered adequate for treating the primary tumor is 40–45 Gy, and for controlling subclinical disease, it is 20–24 Gy, although there are not enough data in the literature to establish a precise dose-response curve [40]. An extensive review of 788 patients with localized pure germinomas treated with RT with exclusive intent and various volumes indicated that the historically applied CSI doses could be excessive [40]. In fact, the percentage of spinal recurrences isolated after whole brain RT (WBI) or ventricular RT (WVI) was 2.9%, while it was 1.2% after CSI, showing a negligible advantage of the latter. The decision for WVI relies on germinomas spreading, as is commonly the case, along the walls of the ventricles [45], instead of local irradiation that was associated with an unacceptable percentage of relapses—up to 23% [40].

Completely replacing RT with chemotherapy has been associated with an unacceptable 50% relapse/progression rate [46] and focal RT with chemotherapy also carried a 10% excess risk of ventricular relapse compared with traditional CSI (5-year EFS 88% vs 97%) [47].

WVI should include the lateral ventricles, third and fourth ventricles, making sure to include the pineal cistern, and the saddle and suprasellar region. Including the prepontine cistern is recommended for large suprasellar tumors and patients undergoing third ventriculostomy (Fig. 2). The WVI volumes must be established by combining the T1 and T2 images obtained on diagnostic MRI with the post-chemotherapy T2 images obtained with the RT CT simulator. The RT volumes must also include any post-chemotherapy residues and exclude any displacements of the pre-chemotherapy brain parenchyma due to the tumor [48].

As for the technique to use, modern methods using photons (IMRT, VMAT, tomotherapy) and protons are both able to cover the ventricular target well. With protons, there is a greater saving of the cerebral and cerebellar cortex, but not of the hippocampus [49]. Beyond the ALARA concept, in a comparison between photons and protons, whether the doses of radiation to the cerebral cortex of 10–15 Gy reportedly administered with modern photon techniques have a real impact from the neuro-intellectual standpoint remains to be seen. In the localized forms of this tumor, neoadjuvant chemotherapy with cisplatinum/etoposide- or carboplatin/etoposide/ifosfamide-based schemes enables a reduction in the volumes and doses of RT: 24 Gy for WVI in fractions of 1.6 Gy plus, only for patients in partial remission (PR) after chemotherapy, a 16-Gy boost to the site of the primitive tumor, for up to 40 Gy in all.

This approach spares the spinal cord and part of the brain, while achieving the same long-term disease control (≈ 90%) [43, 47, 50, 51].

In metastatic forms, the recommended treatment is CSI up to 24 Gy in 1.6-Gy fractions, followed by a 16-Gy boost to the primitive site or macroscopic disease, up to a total dose of 40 Gy. The volumes of CSI are the same as for MB.

In patients without histological diagnosis given neoadjuvant chemotherapy who do not have a CR, a surgical "second look" is generally recommended, providing it carries a low risk of iatrogenic damage. The aim is both to remove any residues and to obtain histological confirmation of suspected non-germinomatous forms.

The non-germinomatous forms respond in fact to platinum-based chemotherapy in proportions between 68 and 78%, but chemotherapy alone is associated with a relapse rate of 50–70% [46, 52, 53]. Non-germinomatous forms require combined treatment as standard. The most often used scheme is called PEI (platinum, etoposide, ifosfamide) for 3 pre-RT cycles [54]. The volumes and doses of RT differ from those used for pure germinomas. For localized disease, RT after chemotherapy involves irradiation of the primitive tumor bed alone up to a total dose of 54 Gy in fractions of 1.8 Gy. In the case of dissemination to the CSF, 30–36 Gy CSI plus a boost of up to 54 Gy to the site of the primitive tumor or any metastases are scheduled, limiting the dose to 50 Gy if there are metastases to the spinal cord.

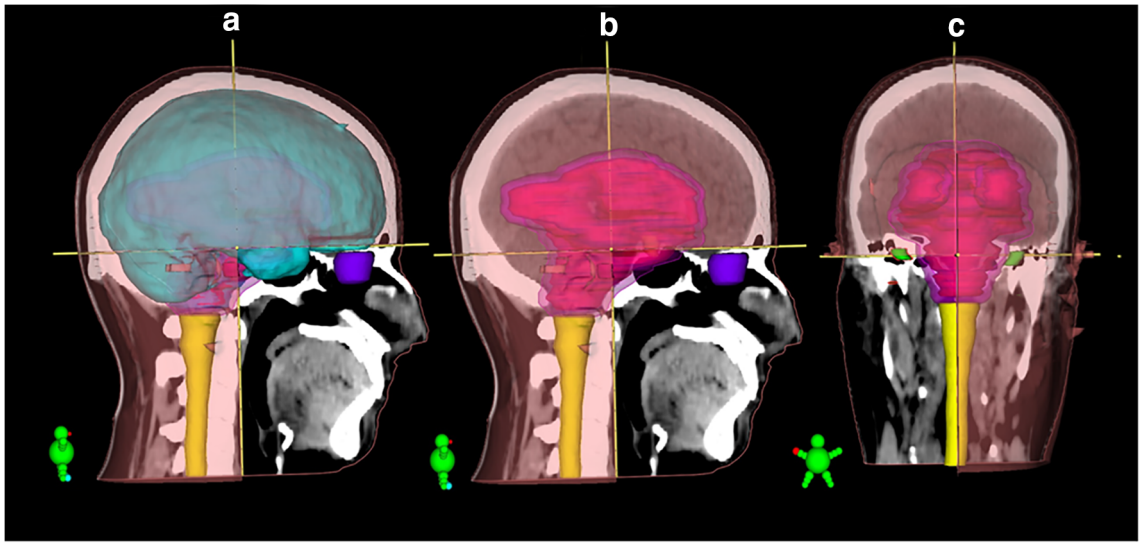

Fig. 2 An adult male patient with localized pure germ cell tumor of the third ventricle, treated with whole ventricular irradiation (WVI). A: total brain volume in cyan; B: planned target volume in pink, clinical target volume in red, enables a significant portion of brain volume to be spared, notably the cerebral cortex and cochleas, the part of the inner ear involved in hearing (C: in green). In this particular case, about two-thirds of the total brain volume can be spared using WVI plus chemotherapy instead of whole brain irradiation alone

Using higher doses of RT in cases where chemotherapy fails to achieve CR is not recommended because the radiologically evident residue is very often not a biologically active tumor but a differentiated form (e.g., mature teratoma) [43]. The long-term survival is 70–80% for localized non-germinomatous tumors and lower for disseminated disease.

In recent years, we have witnessed a tendency to standardize the approach in children, adolescents, and even young adults. All these patients should be treated at centers with experience in this rare and complex disease, however [55].

In pediatric age, given these tumors' great sensitivity to chemo- and radiotherapy, and the greater attention paid to potential late sequelae, the main trials conducted in the USA [53, 56–58], Japan [59, 60], and Europe (SIOP GCT 96) [47] have established that pre-RT chemotherapy (Carbo-PEI with carboplatin, etoposide, ifosfamide) enables the total dose of RT and the volumes of prophylactic irradiation (WVI instead of CSI radiotherapy) to be safely reduced. In association with pre-RT chemotherapy, the RT dose considered "standard" for pure germinoma in children and adolescents is 24 Gy using WVI (while CSI is reserved for metastatic cases), with a boost of 16 Gy to the primitive sites.

In children and adolescents with non-germinomatous forms, the most unfavorable risk factors are alpha-FP levels > 1000, metastases, and tumor residue persisting after induction treatment. This is why a surgical second look is supported in cases with post-chemotherapy residue, providing there is a favorable surgical risk/benefit ratio.

Overall, the median time to relapse is 12 months (range 7–120), but, for the germinomatous forms, it is 50 months [47]. Surveillance should consequently be more intense in the first year and preferably continue up to the 10th year.

Oncological follow-up must include MRI and tumor marker assays also well controlled in the germinomatous forms because of the risk of relapses with a different histology. Patients treated for germ cell neoplasms should be referred to multidisciplinary teams experienced in the treatment of endocrine, neurocognitive, and vascular sequelae (angiomas, etc.) and/or second tumors (meningiomas, second neoplasms induced by etoposide, RT, etc.).

The high incidence of sterility and the long life expectancy for patients with these tumors make it necessary to provide adequate information on the fertility risks (especially for adolescents and young patients). Whenever possible, these patients should proceed to gamete cryopreservation procedures before starting treatment.

Conclusions

Pediatric oncologists rightly worry about the severe neurocognitive late sequelae associated with high-dose CSI, which is why several combinations of systemic chemotherapy with lower doses or volumes of RT have been explored in prospective trials. For some diseases, however, adults with pediatric tumors seem to have a worse prognosis than is usually reported for children and this appeared to be a matter of undertreatment or erroneous treatment, or poor compliance with the therapeutic guidelines [61].

The role of chemotherapy for adults with average-risk MB remains controversial and has yet to be adequately investigated in multinational prospective studies to share the skill of pediatric and adult oncologists [15]. Adult patients' tolerance of chemotherapy following RT is generally lower and these

treatments should therefore be applied at centers with experience in neuro-oncology. More and more reports are pointing to different treatment options for older patients as well, which would probably improve their long-term prognosis and spare them the sequelae of high-dose RT [25, 62–63].

The same can be said for the even rarer category of CNS germ cell tumors, for which "pediatric" protocols generally have any age for inclusion, and should be used to improve adult prognosis and add to our understanding of these diseases.

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Compliance with ethical standards

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

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