Childhood medulloblastoma

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Abstract

Among all the childhood central nervous system tumours, medulloblastoma and other neuroectodermal tumours account for 16–25% of cases. The causative factors of medulloblastoma/PNET have not been well established. It is more frequent in boys than in girls and in children than in adults. There was a significant improvement of survival for children diagnosed in 2000–2002 compared to those diagnosed in 1995–1999. The risk of dying was reduced by 30%. Patients are generally divided into risk-stratified schemes on the basis of age, the extent of residual disease, and dissemination. Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include those in the disseminated category, and in North American trials those that have less than a gross or near-total resection, which is arbitrarily defined as 1.5 cm² of post-operative residual disease. Current and currently planned clinical trials will:

1. evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy boost by the modest intensification of chemotherapy in standard-risk patients;
2. determine whether intensification of chemotherapy or irradiation can improve outcome in patients with high-risk disease;

define molecular and biological markers that improve outcome prediction in patients with medulloblastoma and which can be incorporated for front-line stratification of newly defined risk subgroups.

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1. General information

1.1. Incidence

Among all the childhood central nervous system tumours, medulloblastoma and other neuroectodermal tumours (International Classification of Disease for Oncology, ICD-O 9470/3–9474/3) account for 16–25% of cases [1]. The European annual incidence rate was 6.5 per million children (age 0–14 years) for the period 1988–1997, with no substantial differences between European regions. Incidence was significantly higher in boys than in girls (about 60% boys). The annual incidence rate was higher in children between 1 and 9 years of age (8 per million), slightly reduced in infants (6 per million), and it was lowest in 10–14 aged children (4 per million) [2].

1.2. Survival

Five-year overall survival in children with diagnosis between 2000 and 2002 was 66%, and infants had the worst prognosis. There was a significant improvement of survival for children diagnosed in 2000–2002 compared to those diagnosed in 1995–1999. The risk of dying was reduced by 30% [3].

1.3. Risk factors

The causative factors of medulloblastoma/PNET have not been well established. Since a peak of incidence occurs during childhood, factors operating very early in life might play a key role. Birth weight has often been suggested to be a crude but easily accessible marker of prenatal exposures. Only a small proportion of birth weight is attributable to genetic influences; most of its variance is determined by non-genetic factors, such as maternal nutritional status and body weight, maternal diseases, and environmental exposures during pregnancy. Harder et al. conducted a meta-analysis on the association between birth weight and risk of specific histologic types of primary brain tumours. For medulloblastoma, high birth weight was positively associated with increased risk (odds ratio = 1.27, 95% CI: 1.02, 1.60) [4]. Recent studies have speculated on a potential infectious aetiology. A case–control study in England evaluated various perinatal factors and their impact on childhood brain tumour. The Authors found that the children of mother who had a documented viral infection during pregnancy had 11-fold increased risk of malignant nervous system tumour [5]. A further large population-based case–control study investigated the patterns of day care and early social contacts, as well as other markers of infectious exposure. The results showed a weak positive association between lack of social contact in the first year of life and an increased risk of developing a CNS tumour in childhood. This effect was most prominent in the primitive neuroectodermal tumour/medulloblastoma subgroup (OR 1.78, 95% CI 1.12–2.83) [6]. However, other proxy markers of infectious exposure that were analysed i.e., bedroom sharing, domestic exposure to school-age children, and birth order did not support the hypothesis of a protective effect of infectious exposure. The role of diet, both as a risk and as a protective factor, has been investigated in several studies. Among the most extensively studied hypothe-
2. Pathology and biology

The 2007 WHO classification of CNS tumours recognizes the classic medulloblastoma and the following four variants: desmoplastic/nodular; medulloblastoma with extensive nodularity (MBEN); anaplastic, and large cell [16]. Of these variants, the anaplastic and large-cell medulloblastoma show a certain degree of overlapping and they have been grouped as large-cell/anaplastic (LCA) medulloblastoma in several studies [17]. The frequency of the combined LCA form varies from 10% to 22%.

Nodular/desmoplastic medulloblastoma and MBEN comprise approximately 7% and 3% of all medulloblastoma, respectively. Classic tumours constitute the remainder [18]. Classic medulloblastoma is composed of densely packed cells with round-to-oval or carrot-shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Desmoplastic/nodular medulloblastoma is a variant that contains nodular, reticulin-free zones, or ‘pale islands’ which represent zones of neuronal maturation, exhibits a reduced nuclear:cytoplasmic ratio, a fibrillary matrix and uniform cells with a neurocytic appearance. These nodules are surrounded by densely packed mitotically active cells which produce a dense intercellular reticulin-positive network of fibres. Medulloblastoma with extensive nodularity – (MBEN) occurs in infants and is associated with a good prognosis. It differs from the related nodular/desmoplastic variant by having an expanded lobular architecture, due to the fact that the reticulin-free zones become unusually elongated and rich in neuropil-like tissue.

Such zones contain a population of small cells with round nuclei, which resemble the cells of a central neurocytoma and exhibit a streaming pattern. The internodular component is markedly reduced in some areas.

An interesting issue, recently clarified in the literature, is the frequency of desmoplastic variants and its correlation with age. McManamy et al. reported in 2007 on the UK series (SIOP/UKCCSG PNETsIII): 315 cases >3 years and (SIOP UKCCSG CNS 9204): 35 cases <3 years to clarify this issue. The frequency of the desmoplastic variants of 57% in patients younger than 3 years of age and 5–25% in older children was described. Garrè et al. reported similar numbers in a series of 83 patients treated at a single institution: 52% in patients ≥3 years and 15% (9/57) in older children [19].

The large-cell medulloblastoma is composed of monomorphic cells with large, round, vesicular nuclei, prominent nucleoli and variably abundant eosinophilic cytoplasm. Groups or sheets of these ‘large cells’ tend to mix with cells that have a different morphology characterized by marked nuclear pleomorphism and nuclear moulding. The latter phenotype has been labelled ‘anaplastic’ (Fig. 1).

Large-cell and anaplastic medulloblastoma show considerable cytological overlap. Histological progression over time, from non-anaplastic to anaplastic types has been described in several studies, and a transition can be even observed within a single tumour, as inferred from the pres-
ence of differing degrees of cytological atypia or anaplasia in one tumour [20].

Clinical data strongly indicate a favourable prognosis for the nodular/desmoplastic medulloblastoma [21]. Moreover, comparing the outcome of classic and LCA medulloblastoma, a significantly worse prognosis is evident for the LCA variant [18,22].

Deletions of 17p and isochromosome 17q (i17q), which combines loss of 17p and gain of 17q, have long been recognized as the most common chromosomal alterations in medulloblastoma [23]. The nodular/desmoplastic and LCA variants are also associated with specific chromosomal alterations. Deletions of 9q are observed in up to 40% of desmoplastic medulloblastoma, but occur rarely in tumours of the classic variant, and amplifications of the MYCC and MYCN oncogenes occur predominantly in LCA tumours. The risk stratification of medulloblastoma may be improved by addition of biological markers such as β-catenin, c-myc and trkC [24,25]. Two subsequent papers have in fact outlined the possibility of classifying medulloblastoma patients according to the newly known biological mechanisms, such as MYC amplification that is found in approximately 5–15% of cases, mutations in Sonic Hedgehog (SHH) pathway genes (PTCH1, SUFU) that are found in nearly 25% of medulloblastoma and in WNT pathway genes (β-catenin, APC, AXIN) found in approximately 15% of cases. In both these papers specific genetic signatures were able to both divide medulloblastoma into five distinct subgroups (subgroups A–E) and to assign clinical risk categories to these subgroups, thus outlining the possibility of a better selection and evaluation of patients in clinical trials and supporting the development of new molecular target therapies [26,27].

Tumourigenesis of medulloblastoma is strongly related to deregulation of signalling pathways involved in normal development of the cerebellum. The proliferation of granular cell precursors (GNP) is physiologically regulated by the Sonic Hedgehog (SHH) signalling pathways. SHH is secreted from Purkinje cells in the cerebellum and binds to the Patched (Ptc) receptor on GNPs, which de-represses the Smoothened (Smo) receptor and activates transcription of SHH targets, such as the Gli transcription factors (Gli1). This signalling pathway has also been implicated in the formation of medulloblastoma [28]. There is evidence suggesting that a subset of medulloblastoma cells have a stem-cell like phenotype that drives tumour growth. It has been found that cells expressing the stem-cell marker CD133, obtained from some established medulloblastoma cell lines, have a greatly increased ability to form tumour xenografts [29].

3. Diagnosis

Computerized Tomography (CT) is sometimes the first-line neuroimaging modality for patients with posterior fossa tumours because of its availability in an emergency setting. A typical feature of medulloblastoma seen with CT is a midline, homogeneous, contrast-enhancing cerebellar vermis mass. MRI is, however, a mandatory follow-on imaging, that should be carried out before tumour surgery. MRI features that are typical of medulloblastoma include a heterogeneous hypointense mass on T1-weighted imaging. In contrast to other CNS tumours that show T2-weighted hyperintensity compared with grey matter, medulloblastoma are intermediate between grey and white matter. Contrast enhancement of medulloblastoma is usually heterogeneous. Spinal metastases, which occur in up to 40% of patients, are most commonly seen in the lumbosacral and thoracic areas and are best seen on post-contrast T1-weighted imaging. In doubtful cases they should be confirmed or excluded by axial slices. It is therefore imperative to have an MRI of the spine before starting any adjuvant treatment. Whole CNS imaging should be repeated before defined phases of post-operative treatment [30] as a standard procedure.

Medulloblastoma can be disseminated at diagnosis, and occurs sometimes in the brain with a particular predisposition for subependymal areas of the ventricles. Other imaging modalities such as magnetic resonance spectroscopy (MRS), PET, and single photon emission computed tomography (SPECT) can be helpful to distinguish tumour recurrence from post-therapy necrosis. These imaging modalities might have substantial implications for the future directions of research into medulloblastoma. However, these evaluations are to be considered still investigational.

4. Staging

Staging and subsequent risk stratification are crucial in the management of medulloblastoma. Current staging classifica-
tion requires analysis of the cerebro-spinal-fluid (CSF) and MRI of the brain and entire spine with and without gadolinium. CSF from the lumbar region is preferred because it is a more sensitive medium than ventricular fluid for detecting disseminated disease. CSF should be obtained from the lumbar region 2 weeks post-operatively to avoid a false-positive cytology after the initial resection [31].

Contraindications for lumbar puncture (increased intracranial pressure, etc.) must be considered cautiously. Assessment of the CSF for disseminated disease is crucial, because up to 10% of adults and 30% of children have evidence of disseminated disease at presentation. Traditionally, MB patients are stratified into standard and high-risk groups for therapy according to the clinical presentation, depending on the presence of metastases (M1–M4) or residual disease >1.5 cm² according to North American stratification, as determined by early (within 24–72 h) post-operative MRI [32]. The type of risk group for an MB patient is determined according to Chang’s classification for metastases (Table 1) [33].

Patients are generally divided into risk-stratified schemes on the basis of age, the extent of residual disease, and dissemination (Fig. 2).

<table>
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<th>Table 1 Chang classification for metastases.</th>
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<td><strong>M0</strong></td>
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Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include those in the disseminated category, and in North American trials those that have less than a gross or near-total resection, which is arbitrarily defined as 1.5 cm² of post-operative residual disease (Fig. 3).

Tumour staging will be probably implemented in forthcoming trials through integration with biological findings that have been found in retrospective series to correlate with outcome, such as proteins or genes encoding for neurotrophin-3 receptor, MYC, ErbB2, β-catenin, survivin and p-53 [24,25,34].
5. Prognosis

Today, current treatment protocols that include surgery, craniospinal irradiation, and chemotherapy have achieved 5-year overall survival rates over 70% for standard-risk patients [32].

Until a few years ago, metastatic medulloblastoma series reported dismal results with 5-year survival around 30–50% [35]. Nowadays, intensified chemotherapy regimens (myeloablative schedules with haematopoietic support of peripheral harvested stem cells) and non-conventional radiotherapy schedules seem to have improved prognosis – with 5-year survival rates around 70% – that will need to be confirmed in further trials [36,37].

Similar considerations can be applied to younger children (under 3 or 4–5 years of age at diagnosis, according to national policies) that have traditionally been treated with risk– and age adapted radiotherapy – frequently reducing total craniospinal doses – and prolonged chemotherapy schedules with the aim of reducing late sequelae especially those related to radiation treatment, and therefore reducing the risk of relapse and intensive re-treatment for around 50% of patients [38,39]. The most recent German experience, using systemic chemotherapy schedule combined with intraventricular methotrexate, has resulted in a 5-year progression-free survival of 83% [21], thus demonstrating that a tailored use of drugs is able to replace radiotherapy, at least in some subgroups of patients.

6. Treatment

Current and currently planned clinical trials will:

1. evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy boost by the modest intensification of chemotherapy in standard-risk patients;
2. determine whether intensification of chemotherapy or irradiation can improve outcome in patients with high-risk disease;
3. define molecular and biological markers that improve outcome prediction in patients with medulloblastoma and which can be incorporated for front-line stratification of newly defined risk subgroups.

6.1. Surgery

Surgical resection is a fundamental part of treatment. Depending on the location and dimensions of the tumour, an external ventricular shunt or third ventriculostomy might be needed as emergency treatment, before tumour resection, to decrease intracranial pressure secondary to fluid circulation obstruction at the foramina of Luschka, foramina of Magendie, or the aqueduct of Sylvius. About 20–30% of patients will require a permanent ventriculo-peritoneal shunt consequent to scarring of the cerebro-spinal-fluid pathways. The close relationship of medulloblastoma to the fourth ventricle and sometimes brainstem is a risk for morbidity, but expert pediatric neurosurgeons are frequently able to remove the tumour gross-totally without creating major morbidity, on a type 3 level of evidence [40]. Apart from infections and mechanical complications, such as fluid leak and pseudomeningocele, direct neurosurgical manipulation can cause posterior fossa mutism syndrome [41]. This is characterized by mutism developing 48–72 h after resection, and is associated with severe cerebellar deficits such as dysmetria, hypotonia, paresis, and mood depression, which can last several months. It is probably secondary to disruption of reticular substance pathways.

6.2. Radiotherapy for standard-risk patients

Radiation therapy is the most important adjuvant treatment providing cure, whereas the role of chemotherapy is based on weak data, apart from younger children as it will be below described, and its contribution for cure is in many settings unknown. Until recently, the standard therapeutic approach for standard-risk medulloblastoma has consisted of complete or near complete surgical resection followed by post-operative CSRT. The conventional doses of radiotherapy are around 36 Gy to the craniospinal axis together with a boost of 18–20 Gy to the posterior fossa (total dose 54–56 Gy). Using such doses, various studies have reported that between 55% and 70% of children are alive and free of progressive disease 5 years from diagnosis [42]. It is now clear that a high proportion of survivors of medulloblastoma have significant long-term sequelae. Although some of these late effects are related to the tumour itself, hydrocephalus and the complications of surgery, it is probable that the most important factor in the pathogenesis of these significant sequelae is the dose of craniospinal irradiation needed to treat this disease. Of most concern are the well-recognized neuropsychological sequelae of children receiving cranial irradiation. Several studies have demonstrated marked losses of IQ of up to 30 points or more which are most predominant in young children, particularly those less than 7 or 8 years of age. In addition, it is clear that the majority of survivors suffer significant growth and endocrine dysfunction predominately due to irradiation of the pituitary gland and hypothalamic regions together with the effects of whole spine radiotherapy. Although exact dose effect relationships are not known, there is evidence to suggest that dose reduction might decrease the risk for such hypothalamic-pituitary dysfunctions as well as for decreasing the risk for growth retardation of the spine. With regard to the survival outcome of patients receiving reduced-dose radiotherapy following surgery, pilot data suggested the feasibility of this approach in patients with non-metastatic disease and who underwent gross total resection. Attempts have been made to control tumour growth and to decrease the long-term neurocognitive effects of radiation, especially in young
children by reducing the dose given to the brain and spine [43–46].

After surgical resection, the mainstay for patients older than 3 years at diagnosis is “reduced-dose” craniospinal irradiation (CSI) with a total dose of 23.4 Gy within 40 days plus a localized boost to the posterior fossa up to a total dose of 54–55.8 Gy. This is usually combined with weekly concurrent single-drug – vincristine – and followed by a multi-drug regimen that can be cisplatin, vincristine and lomustine or cisplatin, vincristine and cyclophosphamide, on a type 1 level of evidence [47,48]. Five-year event-free survival based on this regimen is over 80%.

The “simple” regimen of craniospinal irradiation, without the addition of adjuvant chemotherapy, has in fact shown a higher number of early failures when 23.4 Gy was randomized against 36 Gy. These results were not confirmed as statistically significant at a longer follow-up but prompted the premature closure of the study and the addition of chemotherapy in subsequent trials [49].

Further reduction of craniospinal irradiation dose and of posterior fossa boost dimensions is currently under evaluation in a randomized COG (Children Oncology Group) study, and at present is not recommended.

In selecting the total dose of radiotherapy to be delivered to a tumour the aim is to achieve the maximum tumour control with acceptable long-term morbidity. For CNS tumours the important dose limiting tissue is the CNS. For the last 10–15 years it has been accepted that for a given tissue and a given effect in this tissue the shape of the radiation dose–effect curve which most accurately fits in vitro, in vivo and clinical data can be described by the ‘Linear Quadratic Model’ [50]. This model describes the relationship between dose and response for various dose/fractionation regimes. Different types of tissues demonstrate demonstrates a critical different dependence on the fraction size: by decreasing the size of fraction from 1.8 Gy (conventional fraction size) to 1 Gy (as in the proposed hyperfractionated regimens – HFRT) the effects in late reacting tissues (assumed for CNS) are predominantly spared in comparison to effects in early reacting tissues (such as mucosa, bone marrow) and tumours. HFRT involves giving a smaller dose per fraction, with radiotherapy fractions administered at least twice each day. The total radiotherapy dose is increased and the total duration of treatment remains approximately the same. HFRT exploits the differences in repair capacity between tumour and late responding normal tissues such as the CNS. Thus the aim of hyperfractionation is to improve the therapeutic ratio, either by enhancing the anti-tumour effect, without an increase in late effects, or by maintaining the same level of anti-tumour effect without reduction of tumour cell kill.

Hyperfractionated radiation is a technique that, at least theoretically, can achieve increased tumour cell kill with equal effects on critical normal tissues, or reduce normal tissue effects without reduction of tumour cell kill.

A French study on standard-risk medulloblastoma patients treated by hyperfractionated radiotherapy without adjuvant chemotherapy has reached a 3-year progression-free survival of 83% with a good neurocognitive outcome at 3 years of follow-up [51].

Future trials may further evaluate the efficacy and safety of this treatment modality.

Radiotherapy for patients with the diagnosis of a medulloblastoma requires a complex treatment technique. It has been clearly demonstrated that the relapse risk is closely related to the quality of radiotherapy.

The quality control of the radiation technique is considered a fundamental component of any protocol study, particularly in the context of reduced-dose craniospinal radiotherapy (23.4 Gy), where suboptimal radiotherapy may have a greater significance than protocol deviations where 35–36 Gy craniospinal radiotherapy is given. Any targeting deviations are defined as either minor or major: if the quality control is performed online, major advantages derive to patients whose treatment is therefore correctly performed.

6.3. Combined treatment approach for high-risk group patients

As already mentioned in Section 4, patients are stratified for therapy into standard and high-risk groups according to their clinical presentation, depending on the presence of metastases alone (M1–M4) or with post-operative residual disease >1.5 cm². This is based on North American stratification methods [32]. The prognosis for high-risk medulloblastoma is still unsatisfactory. Ever since the 1980s when, whether high-risk or not, medulloblastoma has been treated with a protocol including radiation therapy and chemotherapy (vincristine and CCNU), patients had a better prognosis if they received chemotherapy [35,52]. Chemotherapy is therefore part of adjuvant treatment in this group of patients, on a type 1 level of evidence, but optimal timing and schedule are not yet established.

A single centre study considering the use of RT followed by vincristine, cisplatin and CCNU in high-risk patients reported a survival rate of around 85% [53]. In a SIOP (International Society of Pediatric Oncology) trial open from 1984 to 1989 and published with a 76-month follow-up, 27 metastatic patients treated with standard-dose RT followed by CCNU and vincristine obtained a 5-year PFS of 43% [54]. These results were comparable to the SFOP (French Society of Pediatric Oncology) study, which treated high-risk patients with the “eight-drugs-in-one-day” chemotherapy regimen,
followed by two cycles of high-dose MTX, RT and then further “eight-in-one” chemotherapy [55]. The subsequent French national study confirmed the rate of response to the “sandwich” chemotherapy, but was without any significant improvement in either M1 or M2/M3 patients, who achieved a 5-year EFS of 58.8% and 43.1%, respectively [56]. The Children’s Cancer Group 921 randomized phase III trial, open from 1986 to 1992, also proposed an “eight-in-one” chemotherapy regimen before and after RT. The 83 metastatic patients had a significantly lower PFS than the standard-risk patients (57% M1; 40% M2; 78% NED/M0, p = 0.0006) [57]. In the randomized prospective multi-centre trial HIT ‘91, post-operative neoadjuvant chemotherapy (ifosfamide, etoposide, iv high-dose methotrexate, cisplatin and cytarabine given in two cycles) followed by craniospinal RT was compared to maintenance chemotherapy after immediate post-operative RT (“Philadelphia protocol”). The 3-year PFS for all randomized patients was 65% for M1 patients and 30% for M2–M3 patients, thus achieving a statistically significant difference [58].

More recent studies have produced encouraging results with high-dose chemotherapy and autologous stem-cell transplantation. Strother et al. enrolled 19 patients with metastases for treatment with topotecan, followed by CSI and four cycles of high-dose cyclophosphamide with cisplatin and vincristine, followed by CPC reinfusion. The PFS 2 years after starting the therapy was 73.7 ± 10.5% [59]. This experience was expanded, treating a total of 42 metastatic patients, and obtaining a 5-year EFS of 66% [35]. A preliminary study was conducted on nine patients with supratentorial primitive neuroectodermal tumours and metastatic medulloblastoma who were treated with high-dose cyclophosphamide with cisplatin, vincristine, etoposide and high-dose MTX for 2–3 cycles before radiotherapy. The results were interesting: 7/9 patients were tumour-free after a median follow-up of 27 months [60]. In a more recent trial, open from 1997 to 2003, 21 young patients with high-risk or disseminated medulloblastoma were enrolled for evaluation of their response rate to an intensified induction chemotherapy regimen and single myeloablative chemotherapy cycle with autologous stem-cell rescue. This was followed by RT for patients more than 6 years of age, or with evidence of residual disease on completion of the induction chemotherapy if under 6 years old. The 3-year EFS and OS were 49% and 60%, respectively [61].

The European phase III clinical trial SIOP/UKCCSG PNET-3 ascertained the feasibility of treating high-risk medulloblastoma with neoadjuvant CT (vincristine, cisplatin, etoposide and cyclophosphamide) followed by a standard CSI dose with a posterior fossa boost and/or a boost to metastases. The outcome was rather unsatisfactory in metastatic patients in comparison with earlier multi-institutional series, obtaining a 5-year PFS of less than 40% [62].

Gandola et al. [36] have recently reported on 33 consecutive patients, treated in a semi-institutional setting, receiving post-operative methotrexate (8 g/m²) plus vincristine, etoposide (2.4 g/m²), cyclophosphamide (4 g/m²); and carboplatin (0.8 g/m²) in a 2-month schedule. Hyperfractionated accelerated radiotherapy (HART) was then delivered at a total dose to the neuraxis of 39 Gy (1.3 Gy/fraction, 2 fractions/day) with a posterior fossa boost up to 60 Gy (1.5 Gy/fraction, 2 fractions/day). In cases of persistent disseminated disease before HART, patients were consolidated with two courses of myeloablative chemotherapy and circulating progenitor cell rescue. Otherwise, they received a maintenance chemotherapy with vincristine and lomustine for 1 year. In this series, patients were classified as M1 (9), M2 (6), M3 (17), and M4. Twenty-two of the 32 evaluable patients responded to chemotherapy, disease was stable in 5 and progressed in 5. One septic death occurred before radiotherapy. Eight patients relapsed after a median 12 months. Fourteen of the 33 patients were consolidated after HART. With a median follow-up of 82 months, the 5-year EFS, PFS and OS were 70%, 72% and 73%, respectively. No severe clinical complications of HART have emerged so far. The authors concluded that HART with intensive post-operative chemotherapy and myeloablative chemotherapy proved to be feasible without limiting major toxicity in children with metastatic medulloblastoma.

None of these studies has so far provided more than a type 3 evidence concerning the contribution of high-doses of craniospinal irradiation, possibly delivered through a hyperfractionated/accelerated modality, together with high-dose chemotherapy schedules to achieve better disease control. It is therefore desirable that wider phase 3 trials should be initiated to obtain stronger evidence. Until that time, our recommendations are to enrol these patients in controlled clinical trials, because of the dismal prognosis and the more aggressive treatment required, with accompanying acute and long-term side-effects.

6.4. Treatment for younger children

In the past, the survival of infants with medulloblastoma was inferior compared to older children. Possible reasons that may explain this observation were: delay in diagnosis, increased surgical risk, increased toxicity due to RT, under-treatment, and a potentially “more aggressive” biology. A cut-off age level of 3 years had been introduced in the mid-’80s because strategies to delay or omit irradiation had high priority in order to reduce unacceptable sequelae [37,63–65]. The severe permanent sequelae seen in long-term survivors treated with craniospinal irradiation at a young age, with or without CT, were in fact considered unacceptable. Thus trials were performed in the USA in the 1980s, and then in Europe after 1985 using up-front CT in order to delay or to avoid RT. The MOPP protocol, which was a pioneering project, was used on 12 cases, 8 of whom became long-term survivors [66]. The first Paediatric Oncology baby protocol (POG1), which was the first large cooperative study that attempted to delay irradiation using conventional CT, was followed by several American (Children’s Cancer Study
Group – CCSG) and European (baby protocols of the Société Française D’Oncologie Pédriatique – SFOP, of the Italian Association for Pediatric Oncology – AIEOP, and German Society of Pediatric Oncology and Hematology – GPOH (HIT-SKK ’87 study) cooperative studies [38,65,66–69].

The POG1 study required children <2 years of age to be treated with CT for 2 years, while children who were 2–3 years of age were treated for 1 year. Both groups were eligible for RT at the end of CT. Sixty-two cases were recruited. Event-free survival (EFS) and overall survival (OS) at 5 years were 30% and 69%, respectively. Radical resection was a favourable prognostic factor, as 69% of M0/T0 cases became long-term survivors (13 cases) [68].

The CCSG study tested the “8 in 1” protocol. After a median follow-up of 6 years, a 3-year EFS of 22% was obtained and long-term survival was below 30% in M0/T0 cases [70].

These initial studies showed that only a minority of patients with M0/T0 could be cured with conventional CT, and that the disease could not be controlled in patients with residual tumour after surgery and/or metastases. Therefore, European and American studies intensified systemic CT (POG2), while others added intraventricular CT (Germany) or high-dose systemic methotrexate (Italy – AIEOPSNC9501) [65]. Standard CT in France (Baby SFOP Protocol) included alternating courses of carboplatin/procarbazine, etoposide/cisplatin, vincristine/cyclophosphamide for 18 months. Thirty-three out of 47 MO/T0 patients progressed during/after CT, but OS was 76%. The results in metastatic cases were unsatisfactory (PFS 16%), while localized failures in M0/T0 were successfully rescued by high-dose CT, with or without re-operation, followed by focal irradiation. Neuropsychological outcome was also reported [38].

A German study investigated intraventricular CT in 43 patients. Although this study showed no favourable impact on metastatic disease, it achieved the best known OS and EFS in M0/T0 patients without irradiation (14/17 were cured) [21]. Neuropsychological outcome was better than for cases treated with CSI [63], and about the same as cases treated with systemic chemotherapy alone, or controls. Due to the limited number of cases and special aspects of using intraventricular CT, it remains to be clarified whether these data can be reproduced in a larger international cooperative study.

The introduction of sequential HDCT for relapsed patients or “up-front” for patients with metastases is currently being investigated in the second generation studies, and high response rates have been reported [65,71,72]. The French group has also demonstrated that reduced volumes of irradiation after HDCT contributed to long-term survival [38,72]. Current and future studies should clarify whether these regimens can also increase the proportion of patients that may be cured without RT in the M0/T0 group, as well as in the high-risk group. The Italian AIEOP infant pilot study, which uses HDCT followed either by conformal RT on the residual tumour or by CSI in patients with metastases, shows that 5-year EFS in the first 20 study patients has increased (70%) with respect to previous series where standard-dose schedules were adopted [19,65].

It is still unclear whether the subset of infants that were cured in each study had peculiar biological features that favoured survival. The HIT-SKK ’92 study analysed the impact of the histological variants and reported a high frequency of desmoplastic medulloblastoma (40%).

In addition, the prognosis for desmoplastic medulloblastoma was significantly better compared with classic medulloblastoma [21]. A recent single institution retrospective study reports a similar observation, confirming the high frequency of desmoplastic variants and particularly of MBEN in young ages and the high frequency of association between Gorlin Syndrome and MBEN, which was observed in 40% of cases [19]. Further prospective cooperative studies addressing these issues should be performed.

In conclusion, the treatment of infant MB has evolved (role of RT revisited and more intensive CT adopted) during the last 10–15 years, and survival rates have been improved by modern treatment strategies; recent observations seem to show that age per se is no longer an adverse prognostic factor. This is due to the impact of reserving more intensive treatment for advanced stage disease and unfavourable histology along with the presence of favourable histological variants (in up to 50% of cases).

Many national groups recognize a role for high-dose chemotherapy in delaying or avoiding CSI as a part of multimodal treatment strategy in early childhood medulloblastoma, especially in young children with metastatic or residual disease. The efficacy of such chemotherapy intensification may allow a revised role for irradiation, which may be used with reduced volumes in selected groups of patients when irradiation cannot be safely delayed or avoided (i.e., patients with metastases or unfavourable histology).

Future studies will clarify the prognostic relevance of desmoplasia, post-operative residual tumour and biological markers, in order to improve stratification criteria by risk-adapted treatment recommendations. An international phase III trial for young children with non-metastatic medulloblastoma, comparing survival rates and neurocognitive outcomes of different treatment strategies using standardized criteria, is under discussion within the International Society of Pediatric Oncology (SIOP).

Due to the higher frequency (28%) of cancer predisposition syndromes (mainly Gorlin Syndrome) in young patients [19,73] with medulloblastoma, future trials should include guidelines for the identification of such conditions, and for genetic counselling to families. Due to the increased risk of secondary tumours and the frequency of naevoid basal-cell carcinomas in irradiated fields, every attempt should be made to avoid radiotherapy in infants when associated with Gorlin Syndrome or infants who are at risk of showing it in subsequent years (if presenting with medulloblastoma with extensive nodularity).
7. Late sequelae

Long-term sequelae of patients treated for medulloblastoma, including motor, sensory, endocrinological, cognitive, neuropsychological and behavioural deficits, can markedly affect their quality of life and their re-entry into school and society.

7.1. Endocrine sequelae

The occurrence of neuro-endocrine deficiencies following craniospinal irradiation for medulloblastoma is well known. Surgically induced deficiencies manifest shortly after surgery while radiation-induced damage may manifest months to years after irradiation. For this reason long-term endocrine surveillance after craniospinal irradiation is mandatory on a type 1 level of evidence [74].

Radiation-induced damage is currently considered a consequence of a direct neuronal rather than vascular injury to the hypothalamus on a type 3 level of evidence [75]. Subsequently, due to the prolonged absence of rh-GH-stimulating action, pituitary function may be affected. The hypothalamus–pituitary axis has a different radiosensitivity, with the GH axis being the most radiosensitive followed by the gonadotrophin, ACTH and thyroid-stimulating hormone (TSH) axes.

7.1.1. GH deficiency (GHD)

GHD is observed in 40–80% of survivors of medulloblastoma [76]. Incidence of GHD depends on: age at radiotherapy, total dose delivered (≥45 Gy), fields of radiotherapy, duration, fractions, and time after irradiation. The time interval after the end of treatment and chemotherapy are not determinant in causing GH deficiency. In 1995 Ogilvy-Stuart published final height data in 29 children who had received GH for radiation-induced GHD following therapy for brain tumours and clearly demonstrated the detrimental effect of spinal irradiation and the additive adverse effect of chemotherapy [77]. It worsens with time and frequently becomes irreversible. GHD may develop from 3 months to 5 years after the end of radiotherapy.

Growth screening of irradiated children includes on a type 1 level of evidence [78]: anthropometric measurements (height, weight, BMI, lower segment and arm span, Tanner staging) every 6 months until growth complete and/or sexually mature than once a year (always refer to endocrine, or at least if height/weight2 percentile channels, growth <4–5 cm per year and/or lack of pubertal growth spurt), nutritional evaluation (every 6 months), laboratory tests (IGF-1 – even if its role is debated, IGF binding protein 3, bone age determination, insulin tolerance test and GH provocative tests – sleep, exercise, arginin, clonidine and levodopa).

Once diagnosed, the standard treatment of GHD consists of substitutive therapy with 0.18–0.3 mg/kg somatropin or 0.3 mg/kg somatrem, both daily as a standard option on a type 1 level of evidence. Substitutive therapy is widely considered safe in terms of tumour recurrence and it can be started 1 year after completion of the oncological treatment with no evidence of further tumour growth [79–81].

Three other causes of growth failure must be ruled out before starting GH replacement therapy: (1) slowing of growth during the acute phase of radiotherapy secondary to poor caloric intake, (2) poor spinal (but not limb) growth after radiation of the spine secondary to destruction of growth plates in the spine following spinal irradiation, and (3) premature closure of the epiphyses due to precocious puberty.

7.1.2. Gonadal alterations

Gonadal alterations in children treated for medulloblastoma include: precocious puberty, delayed puberty and hypogonadism.

Incidence depends on: age at treatment (patients treated at younger ages are less susceptible due to sufficient follicular stores [82], concomitant radiochemotherapy, and radiotherapy doses. Gonadal alterations can be demonstrated after 1 year from the end of radiotherapy.

The neuro-oncological evaluation in children with possible gonadal alterations includes on a type 1 level of evidence: yearly estradiol levels assessment and pelvic ultrasonography in females, and yearly testicular volume, testosterone and β-HCG levels in males. For males and females annual height/weight assessment, LH and FSH basal and after GnRH stimulation, bone age, GH levels and Tanner stage should be monitored [83].

Precocious puberty is defined as the development of secondary sexual traits before the age of 8 years in females and 9 years in males accompanied by rapid growth in height; this alteration often coexists with GHD (and in this case if GHD is not treated the child will not benefit of the pubertal growth spurt reaching a short final height). Early detection of precocious puberty is mandatory in order to avoid a short final stature, on a type 1 level of evidence. The treatment of central precocious puberty consists in the administration of long-acting analogs of GnRH agonists, such as leuprolide acetate (1.88–3.75 mg/i.m. monthly) as a standard treatment option.

Delayed puberty must be considered when the patient does not show secondary sexual development by age of 14 for boys and 13 for girls. Replacement therapy might prove useful, and standard treatment options include: conjugated estrogen (0.3 mg) or ethynil estradiol (5–10 μg) orally daily for females and testosterone enanthate (100 mg) once in every 4 weeks for males.

Other detectable alterations in survivors of pediatric medulloblastoma are: infertility and precocious menopause. Sterility is more frequent in males and it is related to alkylating agents. Before treating sexually mature boys/girls with chemotherapy or irradiation, physicians should address the possibility of infertility with patients, including fertility-preservation options and appropriate referral to reproductive specialists [82].
7.1.3. Hypothyroidism

Altered thyroid function during both craniospinal and cranial radiotherapy with central hypothyroidism after radiotherapy has been reported with a prevalence of about 6% [84]. The role of chemotherapy in inducing thyroid damage is debated. Incidence of hypothyroidism also depends on RT fractions delivered.

Hypothyroidism may contribute to growth failure and learning disabilities in survivors. Other symptoms are fatigue, weight gain, cold intolerance, constipation, dry skin, brittle hair and depressed mood. In some studies, most thyroid dysfunctions have been detected within 4 years after radiotherapy. Recommendations for annual screening, on a type 1 level of evidence, include a focused history for symptoms of hypothyroidism, height, weight, skin, hair and thyroid examination, annual bone densitometry, FT4-TSH assessment should be performed every 6 months [83]. The values should be maintained in the upper half of the normal range. Thyroid hormone recommended replacement is made with oral l-thyroxine once daily orally (0.05–0.1 mg), and in case of complete thyroid failure, 4–5 μg/kg/day for children and 2–3 μg/kg/day for adults [85].

7.1.4. Hyperthyroidism

Hyperthyroidism may rarely occur after irradiation for pediatric medulloblastoma. Symptoms include: heat intolerance, tachycardia, palpitations, weight loss, emotional lability, muscular weakness and hyperphagia. Screening for hyperthyroidism consists of yearly physical examination (eyes, skin, thyroid, heart and neurologic examination) and FT3-FT4-TSH assessment [83].

7.1.5. Thyroid nodules

Yearly thyroid physical examination should be performed. Periodical ultrasound examination is required, and fine needle aspiration should be considered in case of suspicious nodules [83].

7.1.6. Hyperprolactinemia

Hyperprolactinemia is a frequent finding after brain irradiation and may be due to the destruction of the hypothalamus–pituitary axis or to primary hypothyroidism. It has been described in both sexes and all age groups, but is most frequently observed in the adult females [75]. It has only been demonstrated more than 2 years after therapy. Screening includes periodic PRL and TSH assays, and when PRL levels are higher than 50 ng/ml a pituitary MRI should be performed. The clinical features of hyperprolactinemia in females include oligomenorrhea or amenorrhea with anovulation or infertility, in males decreased libido and sexual potency with progressive hypogonadism are observed. Galactorrhea is a less frequent finding, and rare in males.

Spontaneous resolution of the hyperprolactinemia at 5–6 years after radiotherapy is a sporadic finding, more often a standard treatment with a dopamine agonists is necessary (Bromocriptine 1.25–5 mg/day orally gradually increasing the dose, or Cabergoline 0.25–1 mg/week orally).

Central adrenal insufficiency ACTH deficiency is rare but potentially life threatening; in one series it has been reported in 24% of pediatric brain cancer survivors, most of whom were medulloblastoma survivors [76]. Symptoms include failure to thrive, anorexia, dehydration, hypoglycemia, lethargy and unexplained hypotension. Laboratory assessments include 8:00 a.m. cortisol dosage. Given that central adrenal insufficiency has been detected in survivors many years after the completion of therapy, an 8:00 a.m. serum cortisol level should be obtained yearly until 15 years off therapy, on a type 1 level of evidence. Further endocrinological evaluations and treatment are needed if cortisol levels are <10 μg/dl [83].

If ACTH deficiency is suspected on clinical grounds, a test of the whole axis, such as the ITT or the metyrapone test should be performed, on a type 1 level of evidence [86].

7.1.7. Osteopenia/osteoporosis

Osteopenia/osteoporosis can be caused by both steroid therapy and craniospinal irradiation while GH deficiency does not seem to be an important factor [84]. The exact mechanism of this radiation-induced osteopenia is yet to be elucidated but appears not to be linked to disturbances in the “usual” hormones – growth hormone, thyroid hormone, and sex steroids. Bone density evaluation by DEXA or quantitative CT should be performed during follow-up, starting at 2 years after completion of cancer therapy. The patient should be referred to a specialist if osteoporosis is suspected (T score ≥ 2.5 DS) or history of multiple fractures [83]. Patients with posterior fossa brain tumours infact, often have balance problems and gait disturbances that may persist after therapy. This increased risk of falling, coupled with a reduction in bone density, may place these patients at considerable risk of fractures. Calcium and Vitamine D supplementation and optimisation of endocrine replacements are important as well, on a type 3 level of evidence [87].

7.1.8. Overweight/obesity, dyslipidemia, and metabolic syndrome

Cranial RT but also the heavy metals carboplatin and cisplatin often used in medulloblastoma may cause dyslipidemia. Concurrent GH deficiency and hypothyroidism may exacerbate overweight/obesity. The survivors follow-up includes annual assessments of blood pressure and body mass index. Fasting blood glucose, serum insulin and lipidic profile should be screened every 2 years in patients who are overweight or obese, and every 5 years in normal weight patients. Other co-morbid conditions such as dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance should be monitored.

Counseling for dietary modification, exercise, and weight loss should be given while a pharmacologic intervention should be considered in patients unresponsive to dietary and lifestyle modifications [83].
7.2. Neurocognitive outcome

Many survivors of medulloblastoma treatment experience long-term cognitive, neuropsychological and academic impairments: cognitive impairments are frequent, and specific neuropsychological deficits affect the later cognitive development and the acquisition of new skills. The ultimate neurocognitive outcome is very complex and depends on a number of factors that interact in unpredictable ways. The functional neurocognitive domains that are affected the most by treatment are: attention, executive functioning, processing speed, working memory and learning, which adversely influence academic performance [88–90]. It is well established, on a type C basis, that children with medulloblastoma demonstrate declines in neurocognitive functioning and academic achievement over time. Because of deficits in these important functional domains, survivors experience declines in Intelligence Quotient (IQ) and academic achievement relative to their same-age peers. This does not mean that the cognitive growth rate is arrested or declines as in dementia, but it is reduced compared with same-age peers.

Therefore, as the time since treatment increases, the gap in abilities between the survivors and the general population increases. This gap challenges some survivors in problem solving, academic achievement, independent living, and the quality of life in general.

In some children the IQ drops by as much as 3–4 points per year: brain calcifications, leucoencephalopathy and reductions in white matter volume correlate with these declines in neurocognitive functioning [88].

The late neurocognitive effects can be caused by any of the treatment modalities; the main risk factors for their onset include:

1. (Younger) Age at diagnosis and treatment. The earlier the brain damage, the worse and more generalized is the cognitive impairment. The brain damage caused by the tumour site, the presence of clinical complications and oncological treatment arrests the physiological development of brain structures and functions, affecting or halting the processes leading to new skills acquisition, with a negative domino effect on cognitive development [91]: there is an evidence on a type C basis;

2. Tumour site (tumour invasion of normal brain/ compression of the tumour on the brain parenchyma and trauma from surgical resection). Because of their location in, or near the cerebellum, cognitive and neuropsychological difficulties may arise from the primary impact of the tumour and surgical resection due to damage to this structure. The cerebellum plays an important role in higher cognitive functions given the reciprocal connections with the frontal lobe, and there can be long-term deficits in speech, language and communication, executive function, visuospatial ability and behavioural regulation [89,92].

3. Clinical complications (hydrocephalus). Posterior cranial fossa tumours, cerebellar and pontine tumours can cause an obstruction of the fourth ventricle with ensuing hydrocephalus. This, in turn, may cause a generalized damage and non-specific cognitive problems that add to the structural and functional damage that is specifically related to the tumour site [93].

4. Cranial radiation therapy (CRT). The most prominent deficits for children with brain tumours are associated with cranial radiotherapy: patients receiving CRT are significantly more likely to have school problems than other brain tumour patients and experience a pervasive decline in knowledge acquisition. Poor intellectual outcome is associated with higher radiation doses and a larger volume as well as younger age at radiotherapy. The effects of CRT begin to clinically impact cognitive functioning at about 1 year post-treatment and show a continuing pattern of decline over time. An analysis of longitudinal changes in IQ scores over time revealed that younger patients experience an immediate decline that continued over time, while older patients experienced a delay in decline for about 2 years [94,95].

5. Sensory and motor impairments. Such deficits heavily impact on the later learning experience and the natural cognitive decline [88].

In general, two processes could account for the cognitive decline experienced by patients with medulloblastoma. Children who show a decline in their standardized IQ scores could be losing previously acquired information as evidenced by a decline in raw scores. They could continue otherwise to acquire new information, but at a rate slower than expected when compared with normal same-age peers, with a decline in standard scores. A slow rate of knowledge acquisition directly affects a patient’s potential academic performance, so these survivors are at great risk of losing the ability to live independent lives. School completion is highly dependent on the achievement of basic academic skills, including reading and spelling [88]. These skills have served as important endpoints in comprehensive studies of cognitive ability following treatment for medulloblastoma [88,96].

Patients younger than 7 years show a greater impairment in reading than patients with an older age at diagnosis. While measures of intelligence and school achievements are important for understanding treatment-related changes, it is evident that changes in more basic cognitive skills such as memory, attention and processing may occur earlier in the cascade of events. In point of fact, attention and behaviour planning and organization as well as the ability to store and organize information are critical prerequisites for knowledge acquisition. It has been speculated that in children treated for medulloblastoma the inability to acquire new information and skills at a rate comparable to healthy same-age peers may be due to deficits in underlying core abilities such as memory, attention and speed of processing.
Given these issues, targeted functional assessments should be carried out periodically, on a type C basis, in order to test for cognitive problems, if any, and start specific rehabilitation together with appropriate school support.

Besides interventions aimed at reducing the neurotoxicity to the CNS, effective intervention programmes may be considered the second line of defence against the cognitive decline following treatment. An early assessment of a child’s deficits and strengths is necessary to help parents and teachers provide proper care, support and recovery from hospitalization.

Generally, children who survive pediatric medulloblastoma are impaired, so they necessitate long-term multidisciplinary follow-up and treatment for psychological–emotional difficulties.

The degree of impairment varies, however, between patients. Patients at heightened risk of developing specific cognitive deficits should be accurately screened to start intervention programs that can include drug therapy, cognitive therapy to enhance attention through metacognitive strategies and cognitive-behavioural strategies, along with personalized educational and support programmes [97].

Furthermore, patients treated for medulloblastoma frequently show psychological and behavioural problems such as inadequate social competence, withdrawal, anxiety and depression that affect social adjustment and interpersonal skills. These emotional and behavioural disorders adversely influence their psychological functioning and quality of life.

Given the complexity and variability of these deficits, a range of rehabilitative services should be offered including speech and language therapy, occupational therapy, physical therapy, psychotherapy and educational remediation. Furthermore, as problems may arise at a later time, regular follow-ups are needed to monitor the children’s cognitive development and school progress.

7.3. Neurosensorial late effects

Auditory deficits are the most frequent late effects and are associated both with cochlear irradiation during boost to posterior fossa and cisplatin use [98]. Hypoacusia can be monolateral or bilateral and so severe as to require hearing aid. Audiometry is therefore constantly required during treatment and with regular follow-up examinations to provide early correction of deficits.

Visual defects relating to acuity are mainly due to intracranial hypertension while, nystagmus and diplopia may be found secondary to mass effects and tumour removal. Other defects, such as dysmetria and ataxia, are frequently ameliorated by early re-education.

7.4. Orthopedic late effects

Craniospinal irradiation is a complex radiotherapeutic technique because of the challenges involved in delivering a uniform dose to the brain and the spinal axis, taking care of the junctions involved and the necessity to involve all the vertebral bodies to prevent deformities deriving from asymmetrical bone growth. Earlier studies have used the sitting and standing height as a composite measure to assess patients’ growth.

Craniospinal irradiation can be a concomitant cause of kyphosis and of vertebral demineralization. This may also be caused by steroidal therapy, GH and gonadotropin deficits, or altered food intake. Vertebral growth is obviously altered by irradiation and not helped by growth hormone replacement [99]. Modeling the radiation related treatment effects such as bone growth in children subjected to CSI is important because it might improve the selection of patients for risk-adapted strategies that seek to reduce the side-effects of treatment. Furthermore the radiation therapist group in St. Jude’s have demonstrated in a very interesting model that all vertebrae grew significantly after craniospinal irradiation, with the vertebrae of the boys and younger patients growing at a rate greater than that of their counterparts. The effect of age was similar across all vertebrae, and female gender had the greatest effect on the growth of the lower cervical and upper thoracic vertebrae [100].

7.5. Second tumours

The use of both irradiation and chemotherapy (alkylating agents, nitrosureas, etoposide) contributes to the occurrence of secondary tumours [101].

Meningiomas, cavernomas and glial tumours are found in radiation fields as long as 30 years after treatment, and justify the prolongation of follow-up.

Secondary tumours due to treatment have to be distinguished from those arising in cancer predisposition syndromes like Gorlin’ and Turcot’s syndromes.

8. Follow-up

Relapses of medulloblastoma occur and more than half of these relapses have a component of disseminated disease. Relapses occur in nearly 75% of pediatric cases within 2 years.

Relapse is most commonly diagnosed by neuroimaging; occasionally, clinical progression precedes neuroimaging findings. There are no formal clinical trials that address the specific question of the frequency of MRI use for radiographic surveillance [102].

Patients enrolled in study protocols have a formal timetable for imaging, although when a patient has completed therapy the intervals between MRI scans become arbitrary. We generally recommend imaging of the brain and spine every 3 months for the first 2 years; later MRI of the brain should be performed every 4 months for the third year, every 6 months until the fifth year and then annually on a type C basis. Evaluation of the spine is generally required only in case of clinical suspicion.
Part of follow-up is all the clinical, radiological and biochemical examinations, together with tailored tests for neuro-functional capabilities as detailed in Sections 7.3 and 7.4.

8.1. Treatment at relapse

The approach to treatment of a patient with relapsing medulloblastoma varies, and depends on a range of factors. First, the age of the patient is important when deciding to use radiation therapy, which can cause severe neurological morbidity in children younger than 3 years old and is therefore avoided at diagnosis in this age category standard-risk patients, but can be used at relapse as retrieval, combined with various chemotherapy schedules mostly with myeloablative dosages [103]. This option, which has been used with some success, is to be considered investigational only and is not successful in older children that have already received craniospinal irradiation. In this age group, in fact, approximately 20% of patients who experience relapse after irradiation cannot be cured by salvage therapy, barring very rare exceptions (<5% of those who experience relapse) [104,105].

In older children who have received craniospinal radiation as part of their initial therapy, re-operation, followed by focal radiation with conformal techniques or proton beam might be an option for solitary recurrences and should be considered on a case-by-case basis [106]. However, in these circumstances, the CSF must be examined before starting therapy to assess the extent of dissemination.

Trials of idarubicin, taxol, topotecan, temozolomide, and irinotecan recorded few responses with nearly all patients developing further tumour progression [107–111]. Another approach under investigation is the use of a low-dose chemotherapy regimen called “metronomic” therapy. Several groups have reported the feasibility of this approach for treating pediatric brain tumours in case series [112] although no formalised clinical trials have been done to date. The main concerns about this approach are the immediate haematological toxicities and the long-term risk of secondary malignancies. More clinical trials are needed to validate this line of therapy which is an investigational only option.

Several drugs act on tumour clonal cells, but not on tumour stem cells, which seem more resistant to multi-drug therapy. The goal of the new targeted molecular therapy will be to eliminate tumour stem cells that are present in the tumour bulk. The identification of activated signalling pathway components of stem cells may help to define new treatment strategies in aggressive tumours such as relapsed medulloblastoma (Fig. 4).
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Conflict of interest statement

Authors have no conflict of interest to be disclosed.

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the START project. The START Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in Ann Oncol 1999; 10: 769-774.

- **STANDARD** ("standard", "recommended" [or "not recommended"])
  This can be considered a conventional choice for the average patient.

- **INDIVIDUALIZED** ("suitable for individual clinical use")
  This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.

- **INVESTIGATIONAL ONLY** ("investigational")
  This is something which, in principle, can be offered to the patient only within a clinical study.

**TYPE of OPTION**

- **TYPE C basis** (General consensus)
  There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed.

- **TYPE 1 evidence** (Randomised trial(s) available, strong evidence)
  Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.

- **TYPE 2 evidence** (Randomised trial(s) available, weak evidence)
  One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.

- **TYPE 3 evidence** (External controlled comparisons available)
  Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.

- **TYPE R basis** (Rational inference)
  Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).
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