1. GENERAL INFORMATION

1.1 General information

1.1.1 definition
Medulloblastoma is a highly cellular malignant embryonal neoplasm classified as a Primitive Neuroectodermal Tumour (PNET) (Kleihues 1993). It is the most common malignant brain tumour in childhood, accounting for between 15 and 25% of all childhood primary central nervous system (CNS) neoplasms (Peris-Bonet 2006). By definition, medulloblastoma arises in the posterior fossa, usually from the cerebellar vermis in the roof of the 4th ventricle (see Figure 1). As with other PNETs, medulloblastomas have a marked propensity to seed within the CSF pathways, with evidence of such metastatic spread occurring in up to 35% of cases at diagnosis (see Figure 2).

Figure 1
Medulloblastoma with typical location within the posterior fossa in a 8 year old boy. Axial MRI, T1 weighted Gadolinium contrast enhancement

Figure 2
Medulloblastoma with metastatic spread to the meninges within the posterior fossa and with a large intramedullary deposit. Sagittal and axial MRI, T1 weighted Gadolinium contrast enhancement

1.1.2 General data on stPNET
Supratentorial PNET (stPNET) is a extremely rare disease, therefore it is currently difficult to define guidelines for diagnosis and treatment. However some data do exist for children which may serve as a
basis for defining general disease management in adults. These tumours arise preferentially in the hemispheres or in the pineal region (pinealoblastoma).

1.2 Incidence

Medulloblastoma and Primitive Neuroectodermal Tumours of brain (PNET) (International Classification of Disease for Oncology, ICD-O 9470/3-9474/3) (ICD-O 2000) are rare tumours. The European annual incidence (world-standardised) is about 1.1 per million in the male and 0.8 per million in the female adult population (Parkin 2002). These neoplasms are typically seen in children, about 70% of all cases being diagnosed in patients under 15 years of age. The peak age at presentation is children 3-6 years aged, with only 25% of patients being between 15 and 44 years of age (Peris-Bonet 2006). PNET occurs twice as frequently in males than in females (Parkin 2002) (see Figure 3). Rising incidence was recorded for PNET in European children and adolescents: the rates increased on average of 1.3% during the period 1978-97 (Peris-Bonet 2006). The yearly incidence in the European children was 6.5 per million (Peris-Bonet 2006) and decreases with increasing age to 0.5 million per year (Parkin 2002). In the world, there are some differences: high incidence (more than 1 million year) were observed in Columbia (Cali), Australia (Victoria), Denmark, Canada, Israel and the Netherland (see Figure 4).

Figure 3
Survival data for patients with PNET are available from the population-based cancer registries of about 20 European countries in the EUROCARE study (Verdecchia 2007). The survival analysis covered 867 adults

Figure 4
Cancer incidence rates (world standardised, cases per million per year), in fifteen male adult (> 15 years of age) populations (Source: Cancer Incidence in Five Continents, vol.VIII)

1.3 Survival

Survival data for patients with PNET are available from the population-based cancer registries of about 20 European countries in the EUROCARE study (Verdecchia 2007). The survival analysis covered 867
adults diagnosed with PNET of the brain, during the period 1995-2002 and followed-up until 2003. Relative survival analysis among those adult patients was 78% at one year, 61% at three years and 52% at five years, with no gender differences. Five-year relative survival decreased with age from 56% in the youngest (15-44 years) age groups to 9% in the older group of patients (45 years and over). The five-year survival analysed in 1,050 European patients diagnosed during 1987-2002 showed no significant change over the period.

Acknowledgment
The authors thank the members of the EUROCARE Working Group for their permission to use the survival analysis from the EUROCARE dataset.

### 1.4 Risk factors

The causes of medulloblastoma/PNET have not been well established. PNET is more frequent in males than in females and in children than adults. Some genetic syndromes are known to greatly increase the risk of PNET, including Turcot syndrome (in association with familial polyposis colon cancer) and nevoid basal cell carcinoma syndrome (associated with PTCH germline mutations)\(^{(Stewart 2003)}\). These mutation are rare and account for fewer 5% of all cases. Also, ionizing radiation (Shore 2003) are known to increase the risk of brain tumour. Low dose radiation treatment of tinea capitis and skin disorders in children increases the risk of CNS tumours well into adulthood, as does radiotherapy for childhood cancers and leukaemia. Few epidemiological studies have addressed the potential role of viruses in causing brain malignancies. Polyomaviruses, including JC virus (JCV), BK virus (BKV), and simian virus 40 (SV40) have attracted much attention in the past decade due to their being isolated repeatedly from various human tumours, including those originating from the central nervous system (CNS). JCV DNA sequences have been isolated from a number of human CNS tumours, including medulloblastoma \(^{(Croul 2003)}\).

### 2. PATHOLOGY AND BIOLOGY

The histogenetic origin of medulloblastoma is a controversial issue. It appears that the desmoplastic variant originates from specific cerebellar progenitor cells. These are often correlated with the neurotrophin receptor p75NTR, which is rarely observed in classical childhood medulloblastoma, suggesting that the desmoplastic variant is a different tumour type \(^{(Bühren 2000)}\). Additionally, other molecular genetic investigations indicate that these tumours display a different pathogenesis \(^{(Pietsch 1997; Sarkar 2002)}\).

In particular, amplification and overexpression of MYC and MYCN occurs in 5-10% of medulloblastomas. Some authors have examined the expression of MYC mRNA and related it to clinical outcome: increased levels of MYC expression have proved to be a significant predictor of worse outcome \(^{(Herms 2000; Grotzer 2001)}\). Other frequent genetic alterations in medulloblastomas regard chromosome alterations, in particular on chromosome 17. Deletions of the short arm of this chromosome occur in up to 40-50% of primary tumors. Several authors observed that chromosome 17p deletion was correlated with a worse prognosis, even if this correlation was not always statistically significant \(^{(Batra 1995; Biegel 1997; Cogen 1996)}\). Other frequent non random chromosomal abnormalities detected in medulloblastomas include gains of chromosome 1 and 7 and loss of 1p, 3q, 6q, 9q (locus of PTCH gene), 11p, 11q and 16q \(^{(Brandes 2003)}\). Moreover, loss of heterozygosity (LOH) for a specific region in chromosome 9q have been found in medulloblastomas characterized by a desmoplastic phenotype \(^{(Schofield 1995)}\). The tendency for metastatic spread is much lower in adults than in children (8 and 13% respectively in two series of adult patients) \(^{(Frost 1995; Carrie 1994)}\). However, late relapses are common. This can be seen in the series reported by Frost et al, where the 5 year overall survival rate was 62 %, which had decreased to 41% after ten years. Similarly, Chan et al observed a 5 year overall survival of 83 % which had decreased to 45 % by 8 years \(^{(Chan 2000)}\).
Metastatic spread outside the central nervous system is a rare event. Osseous metastases are the most common features both in adults and in children accounting for 80% of metastases outside the central nervous system (Rochkind 1991). The authors also found that lung metastases are higher in frequency in adults as compared to children whereas metastatic disease to the liver occurs more frequently in children; the interval between treatment and diagnosis of metastases is shorter in children (20 months) as compared to adults (36 months). Ray et al (Ray 2004) showed that tissue microarray assayed for immunohistochemical expression of MYC, p53, PDGFR-alpha, ErbB2, MIB-1, and TrkC and for apoptosis combined with clinical characteristics (i.e. presence of metastatic disease) was able to quantify risk in pediatric medulloblastoma patients. In the pediatric medulloblastoma setting, Pomeroy et al (Pomeroy 2002) studied gene expression profile using oligonucleotide microarrays, demonstrating that outcome predictions based on gene expression (with a model made up of eight genes) was statistically significant: patients with a good prognosis pattern, had a 5-year OS of 80% compared with 17% for those with poor outcome pattern. In another study of gene expression profiles, MacDonald et al (MacDonald 2001) described that the PDGFR-alpha and the Ras/mitogen-activated protein (MAP) kinase pathway genes were significantly upregulated in metastatic (M+) tumors but not in nonmetastatic (M0) MBs, This finding suggests that the PDGFR-a and Ras/MAP kinase signal transduction pathway may be rational therapeutic targets for M+ disease.

3. DIAGNOSIS

The predominant clinical symptom of medulloblastoma of the 4th ventricle and vermis is increased intracranial pressure, especially when the tumour is obstructing the flow of CSF, thereby causing hydrocephalus. Nausea and vomiting are also common. Ataxia may also be seen and is often misinterpreted. Palsy of the cranial nerves indicates infiltration of the floor of the 4th ventricle and spinal metastases may cause neurological deficits related to the sites of the lesions. Nystagmus and abnormalities of extraocular movements are also common findings. Diplopia generally represents impairment of cranial nerves IV or VI. Other focal neurologic deficits such as hemiparesis, hearing loss, and seventh cranial nerve palsies occur less often.

4. STAGING

Precise staging is indispensable for distinguishing between standard- and high-risk patients, because modern treatment concepts are based on the prognoses of these different patient groups including children and adults.

**Standard:**
Diagnostic imaging with MRI (magnetic resonance imaging) should be performed before surgery in order to produce a clear delineation of the tumour. CSF cytology and MRI of the spinal canal are necessary to detect possible metastatic spread. Surgical information and imaging data allow staging to be carried out according to the Chang staging system (see below).

**Figure 5 - Chang classification system for medulloblastoma**

<table>
<thead>
<tr>
<th>Tumour size and extent of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
</tr>
</tbody>
</table>
**T2**  
Tumour e 3 cm in diameter and further invading one adjacent structure or partially filling the fourth ventricle

**T3a**  
Tumour further invading two adjacent structures or completely filling the fourth ventricle, with extensions into aqueduct or foramina of Magendie or Luschka with marked internal hydrocephalus

**T3b**  
Tumour arising from the floor of fourth ventricle or brain stem and filling the fourth ventricle

**T4**  
Tumour penetrates aqueduct to involve third ventricle or midbrain or extends to cervical cord

**M0**  
No metastases

**M1**  
Microscopic evidence of tumour cells in cerebrospinal fluid (CSF)

**M2**  
Macroscopic metastases in cerebellar and/or cerebral subarachnoid space and/or supratentorial ventricular system

**M3**  
Macroscopic metastases to spinal subarachnoidal space

**M4**  
Metastases outside the central nervous system

**Suitable for individual clinical use:**  
CT (computerized tomography) and myelography can be performed for staging purposes if there is no access to MRI or if the patient's condition does not allow MRI.

**Investigational:**  
The role of PET (positron emission tomography) is unclear and should be reserved for investigational purposes.

Regarding local disease, several recent series have demonstrated the prognostic importance of achieving a total or near total surgical excision (Albright 1996). This was clearly demonstrated by the Children’s Cancer Group (CCG).

top

5. **PROGNOSIS**

The prognosis for both children and adults is based essentially on the extent of disease. Risk factors include initial tumor size, brainstem infiltration, postoperative residual tumor and metastatic disease, but the definition of standard (or average) and high risk groups, respectively, is inconsistent in literature. Some authors considered standard (or average) risk patients those with residual tumor of <1.5 cm2 and no metastatic disease (Packer 2003; Tabori 2006) while others included also T stage into risk assessment, considering T1-T2 and T3a into standard (or average ) risk group (Brandes 2003). Prados et al analyzed 47 patients and found a five-year progression-free survival for standard risk patients of 54%, compared to 38% for high-risk patients (Prados 1995). The influence of metastatic disease is unclear. Frost et al reported a 5-year progression-free survival of 42% in patients without metastatic disease whereas none of the patients with metastases survived (Frost 1995). In the series of Chan, the 5-year progression-free survival was 47% as compared to 59% in patients without tumour dissemination (Chan 2000). Despite early data by the prospective series of Brandes et al, suggested that patients without metastases showed a significantly better outcome than those with metastatic spread, (75% showing progression-free survival at 5 years vs. 45% respectively (p = 0.01) - Brandes 2003), more recent data on the same population, after a median follow up of 7.6 years, showed that this difference have been lost being progression-free survival at 5 years 61% and 78% in metastatic and no metastatic patients, respectively (p=N.S.) (Brandes 2007). These data were consistent with those by Carrie et al., that could not detect an impact of metastatic disease on prognosis (Carrie 1994). In their study, the 5-year survival rates were 51% for patients with metastases and 58% for metastases-free patients which was a statistically insignificant difference. The prognostic relevance of postoperative residual disease is also a controversial issue. Carrie
et al analyzed 156 patients without showing an impact of residual tumour on survival (Carrie 1994). The 5-year progression-free survival rate was 59 % in 109 patients without residual disease, compared with 64 % in 50 patients with residual tumour. By contrast, Chan observed a 5-year progression free survival rate of 86 % for 17 patients without residual tumour versus 27 % for patients with residual tumour (Chan 2000). In a large retrospective series Padovani et al analysed 253 patients showing that brainstem and fourth ventricle involvement, and dose to the PCF were negative prognostic factors in a multivariate analysis (Padovani 2007). Data from the updated analysis performed by Brandes et al, showed that postoperative residual disease did not impact significantly on the 5-year progression-free survival, while T status showed a border line correlation with 5-year PFS being, 82% in patients with T1 - T3a disease and 44% in patients with T3b - T4 disease (P =0.06) (Brandes 2007). In stPNETs, despite the use of the same treatments used for medulloblastoma, the survival after combined radio-chemotherapy is 20 to 30% worse compared to results obtained in patients having tumours within the posterior fossa (Cohen 1996). In the HIT 88/89 and 91 trials a progression-free survival at 3 years of 39.1% was achieved in 63 children (see Figure 10). Radiotherapy of the craniospinal axis with a sufficient dosage to the primary tumour site (/> 54 Gy) and within the adjuvant regions of the neuraxis (/> 35 Gy) is crucial to optimal outcome. In 48 patients receiving treatment according to the protocol guidelines the 3-year progression-free survival was 49.3 % (see Table 1) (Timmermann 2002).

Table 1 - Univariate analysis of correlation between radiotherapy parameters (major violations) and progression-free survival rates in 63 children with stPNET (HIT 88/89 and 91) [33]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pat.</th>
<th>3 y. PFS</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>7</td>
<td>143</td>
<td>0-40.2</td>
<td>0.0012</td>
</tr>
<tr>
<td>Local+Csi</td>
<td>54</td>
<td>437</td>
<td>30.3-57.1</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 54 Gy</td>
<td>10</td>
<td>10,0</td>
<td>0-28.6</td>
<td>0.0045</td>
</tr>
<tr>
<td>*/= 54 Gy</td>
<td>53</td>
<td>447</td>
<td>31.1-58.2</td>
<td></td>
</tr>
<tr>
<td>Dose, CSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 Gy</td>
<td>6</td>
<td>0</td>
<td></td>
<td>0.0051</td>
</tr>
<tr>
<td>*/= 35 Gy</td>
<td>48</td>
<td>493</td>
<td>35.6-63.7</td>
<td></td>
</tr>
</tbody>
</table>

In the HIT 88/89 and 91 study, after a median follow up of 31 months, the local relapse rate was 71%, indicating that local tumour control is of particular importance. Local dose escalations seem to be feasible in order to achieve the higher rate of local tumour control that was seen in some series, however patient numbers were small. Halperin et al., treated 5 patients: 4 are in continuous complete remission and 1 is alive with stable disease (Halperin 1993). This concept is currently under investigation in Germany (Kortmann 2000).

5.1 Differences between adults and children

Medulloblastoma in adults differs from that in children in terms of:

1. Location of tumor (see Table 1)(see Figure 1). In children medulloblastoma frequently arise in the midline at the floor of the 4th ventricle and vermis, whereas in adults the cerebellar hemispheres are primarily involved.
Table 2 - Distribution of histological subtypes and tumor location in adult medulloblastoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Patients</th>
<th>Histology</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haie et al. 1985</td>
<td>1961-82</td>
<td>20</td>
<td>10/9</td>
<td>6/11</td>
</tr>
<tr>
<td>Pobereskin et al.1986</td>
<td>1961-82</td>
<td>12</td>
<td>10/2</td>
<td>4/10</td>
</tr>
<tr>
<td>Bloom et al. 1989</td>
<td>1952-81</td>
<td>47</td>
<td>20/34</td>
<td>20/27</td>
</tr>
<tr>
<td>Cornu et al. 1990</td>
<td>1979-88</td>
<td>24</td>
<td>13/11</td>
<td>9/14</td>
</tr>
<tr>
<td>et al. 1991</td>
<td>1959-88</td>
<td>32</td>
<td>29/3</td>
<td>14/14</td>
</tr>
<tr>
<td>Ferrante et al. 1991</td>
<td>1957-88</td>
<td>32</td>
<td>26/5</td>
<td>12/11</td>
</tr>
<tr>
<td>Carrie et al. 1993</td>
<td>1975-90</td>
<td>30</td>
<td>15/15</td>
<td>15/15</td>
</tr>
<tr>
<td>Aragones et al. 1994</td>
<td>1974-91</td>
<td>30</td>
<td>24/6</td>
<td>11/13</td>
</tr>
<tr>
<td>Ildan et al. 1994</td>
<td>1981-91</td>
<td>11</td>
<td>7/4</td>
<td>7/4</td>
</tr>
<tr>
<td>Peterson et al. 1995</td>
<td>1981-95</td>
<td>45</td>
<td>36/9</td>
<td>17/12</td>
</tr>
</tbody>
</table>

Figure 1

Medulloblastoma with typical location within the posterior fossa in a 8 year old boy. Axial MRI, T1 weighted Gadolinium contrast enhancement

2. Histopathological subtype (see Table 2) In children the majority of histological subtypes consist of the classical variant. In adults, however, the desmoplastic variant is frequently found (up to 50-70% in some series) (Bloom 1990; Carrie 1993; Sheikh 1994).

3. Lesser frequency of metastatic disease. In children the incidence of metastatic spread although varying between the authors is often exceeding 20%. In adult series the incidence was 8 to 13%. However, with improved diagnostic tools like modern neuroimaging the true incidence might become...
higher.

4. **Incidence of late relapses.** In the prospective paediatric trials of the 80ties and 90ties the progression-free survival curves reached a plateau after 3 to 4 years and late relapses were uncommon. In adult series, however, these plateaus are normally not observed. These observations suggest a difference in biological properties.

5. **Type of metastatic spread.** In adults the relative contribution of lung metastases is higher and of liver metastases lower than in children. Additionally, the interval until diagnosis is considerably longer in adults.

6. **TREATMENT**

In the past, adult patients with medulloblastoma were frequently treated according to paediatric protocols, but with varying regimens, under the assumption that the tumours display the same properties in adults as in children. Prospective controlled trials are lacking and current experience is based exclusively on retrospective studies. These comprise small patient numbers and have utilized varying treatments spanning decades during which diagnostic procedures, neurosurgical skills and radiation therapy techniques have changed considerably. Due to the paucity and heterogeneity of data the identification of prognostic factors and the definition of a standard treatment is impossible.

6.1 **Neurosurgery**

The crucial role of surgical resection in patients with medulloblastoma is now well recognised on a type C basis ([Tomita 1998](http://www.startoncology.net/site/index.php?view=article&catid=37:br...)). As discussed above, the extent of surgical resection is an important factor in relation to survival on a type 3 level of evidence. For this reason, neurosurgeons, aided by modern technological adjuncts, make considerable efforts to achieve complete or near complete resection. Today developments in neurosurgical skills have increased the proportion of completely or nearly completely resected tumours and peri- or post-operative complications and neurological deficits resulting from surgery have become rare events.

Investigational therapeutic options:
Few data on the side-effects of surgery exist and in particular there have been no large prospective studies of the sequelae of surgery in patients treated according to a set strategy.

6.2 **Radiation therapy**

Radiotherapy after surgery is the standard treatment on a type C basis. It was accepted as most effective treatment when in 1930 Cushing first reported its decisive role in the curative management of medulloblastoma ([Cushing 1930](http://www.startoncology.net/site/index.php?view=article&catid=37:br...)). In 1953, Paterson noted the necessity for craniospinal irradiation (see Figure 6 and Figure 7), the need for precise coverage of the target volume, and the employment of a sufficient dose to achieve better results in medulloblastoma treatment ([Paterson 1953](http://www.startoncology.net/site/index.php?view=article&catid=37:br...)).

**Figure 6**
**Irradiation of neuraxis. Conventional technique / patient positioning**

**Figure 7**
**Schematic display of craniospinal irradiation for medulloblastoma**
Craniospinal irradiation is followed by a boost to the posterior fossa, which nowadays is performed using modern 3 dimensional treatment planning systems in order to spare normal tissue (see Figure 8).

**Figure 8**
3D treatment planning to boost the posterior fossa

Over the past 40 years there has been progressive improvement in outcome resulting in the current long-term survival rate of 60 to 70% in children and adults. In adults, surgery alone is associated with a high relapse rate and requires adjuvant radiation therapy. Hubbard et al reported 6 spinal recurrences in 8 patients undergoing surgery alone (Hubbard 1989). Ferrante analyzed 32 patients and showed that additional radiation therapy increased survival from 6.5 months to 6.6 years on a type 3 level of evidence (Ferrante 1991). The dose-response relationships for treatment of tumours located within the posterior fossa have clearly been documented (Berry 1981; Bloom 1990; Kortmann 2001). Berry et al noted a 10-year disease-free survival of 77 % if the dose to the posterior fossa exceeded 52 Gy. Lower doses were associated with a 5 year survival rate of 47 %. In adults, Hazuka et al. noted a tumour control of 75 % in the posterior fossa after 55 Gy or more, compared to 40 % tumor control if doses less than 50 Gy where given (Hazuka 1992). Abacioglu and colleagues confirmed these observations on a type 3 level of evidence; the corresponding 5-year control rates being 33 % after doses of less than 54 Gy, as compared to 91 % in patients receiving higher doses (Abacioglu 2002). Dose reductions in the adjuvant areas of the neuraxis appear to be critical. According to the CCSG-experiences (Children's Cancer Study Group) dose reductions from 36 to 23.4 Gy were associated with a significantly increased risk of recurrences outside the posterior fossa on a type 1 level of evidence (Thomas 2000). In combination with chemotherapy however, these dose reductions appear to be feasible (Packer 1999). In this setting a 5-year progression-free survival rate of 79 % was achieved. For adults, only the data of Bloom are available, on a type 3 level of evidence (Bloom 1990). An increased relapse rate after dose reductions from 32 - 35 Gy down to 15 - 25 Gy was observed, on a type 3 level of evidence. Recently, Packer et al. showed an encouraging event free survival (EFS) rate for children with nondisseminated MB treated with reduced-dose radiation (craniospinal irradiation, 23.4 Gy with a boost up to 55.8 Gy to the posterior fossa) followed by adjuvant chemotherapy (lomustine, cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine) (Packer 2006). In the up-dated French series from 1994 for adults radiation therapy at reduced doses in conjunction with chemotherapy yielded identical results as compared with standard dose radiotherapy alone (Padovani 2007). A French Phase II study investigated radiotherapy
alone using hyperfractionation followed by a dose escalating boost in children and achieved similar results as compared with conventional dose prescription in combination with chemotherapy (Packer 2006; Carrie 2005). With a median follow-up of 45.7 months, the overall survival and progression-free survival rate at 3 years was 89% and 81%, respectively (Carrie 2005). However, because of the differences in terms of long-term toxicities between adult and pediatric patients, this approach has not been proposed for adult patients. It has yet to be established whether adjuvant chemotherapy should be added to radiotherapy in adult average-risk patients, because 70 to 80% of these patients are progression free at 5 years with radiotherapy alone (Tabori 2006; Brandes 2007), and hematological toxicities in adult patients are consistent (Tabori 2005; Greenberg 2001).

Investigational options
Recent advances in radiotherapy techniques have sought to improve the therapeutic ratio in childhood medulloblastoma by introducing potentially more effective treatments in ways that will increase tumour control and limit radiation toxicity. They take advantage of high precision treatment techniques as well as fractionation schedules which exploit the radiobiological properties of tumour and normal tissue. These initiatives, however, should be restricted to clinical trials in the paediatric population. Quality control programmes are indispensable to assure precise and reproducible treatment (see Table 3).

<table>
<thead>
<tr>
<th>Author/study</th>
<th>Pat.</th>
<th>&quot;low quality&quot;</th>
<th>&quot;high quality&quot;</th>
<th>Survival</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packer et al., 1991</td>
<td>108</td>
<td>RT 1975 -82 n=67</td>
<td>RT 1983-89 n=41</td>
<td>49% vs.82% 5-y PFS</td>
<td>Significant P=0.004</td>
</tr>
<tr>
<td>Graben bauer et al., 1996</td>
<td>40</td>
<td>RT before 1980</td>
<td>RT after 1980</td>
<td>5-y overall survival 64% versus 80%</td>
<td>Significant p=0.02</td>
</tr>
<tr>
<td>Miralbell et al.1997</td>
<td>77</td>
<td>36 inadequate &quot;helmet-technique“</td>
<td>41 adequate &quot;helmet-technique“</td>
<td>5-y PFS 94 % versus 72 %</td>
<td>Significant p=0.016</td>
</tr>
<tr>
<td>Carrie et al., 1999</td>
<td>169</td>
<td>Min. viol. :67 (40%) Maj. Viol. :53 (31%), Of these : 36 one maj. viol. 11 two maj. viol. 6 three maj. Viol.</td>
<td>49 (29%)</td>
<td>3 y. relapse rate 33% : all patients 23% : corr. treatment 17% : one maj. viol. 67% : two maj. viol. 78% : three maj. viol.</td>
<td>Significant. p=0.04</td>
</tr>
<tr>
<td>Packer et al., 1999</td>
<td>63</td>
<td>Violations : 20</td>
<td>No viol.: 43</td>
<td>5-y PFS 81% vs. 70%</td>
<td>Not Significant p=0.42</td>
</tr>
</tbody>
</table>

6.3 Quality of radiation therapy

The quality of radiation therapy has an impact on treatment outcome on a type 3 level of evidence (see Table 3). The development of modern technologies and the introduction of quality assurance programmes have highlighted the necessity for precise and reproducible irradiation schedule in
medulloblastoma. Grabenbauer et al., noted an increase in survival during the last decades and concluded that the use of modern techniques in recent years has allowed better overall radiotherapeutic management (Grabenbauer 1996). Miralbell et al., analysed the precision of treatment techniques and the impact on survival (Miralbell 1997). They detected that inadequate field alignment in whole brain irradiation was associated with a significantly worse survival. Carrie and co-workers performed a detailed analysis of treatment techniques with special attention to coverage of clinical target volume in SFOP protocols (Carrie 1999). They noted an increased risk of relapses with increasing frequency of protocol violations. In the German HIT study detailed radiotherapeutic guide-lines were given in the protocol. Checking radiotherapy documentation revealed a high degree of adherence to the guidelines, and consistency between their recommendations and the actual treatment delivered. It was concluded that the high quality of treatment was a major contributing factor to the overall outcome, which was in the range of 80% for standard risk patients (Kortmann 1999; Kortmann 2000).

6.4 Chemotherapy in standard risk medulloblastoma

Previous randomized series in children could not demonstrate a survival benefit for the use of additional chemotherapy on a type 1 level of evidence (Tait 1990; Evans 1990; Bailey 1994). In the recently published SIOP III trial (Société Internationale d’Oncologie Pédiatrique), however, additional chemotherapy achieved a statistically significant superior event-free and overall survival compared to radiotherapy alone, on a type 1 level of evidence (Taylor 2003). By contrast, the role of chemotherapy in adults is far from clear. The 5 year overall survival rates in retrospective studies vary between 26 and 83% independent of additional chemotherapy (see Table 4).

Table 4 - Medulloblastoma in adults: treatment outcome in retrospective studies. OS : Overall survival, PFS : progression-free survival, DFS : disease-free survival, CSI : craniospinal irradiation, n.d. : no data

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>RT</th>
<th>Chemotherapy</th>
<th>Age</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farwell</td>
<td>44</td>
<td>60% of pat. surgery + rad.</td>
<td>No ChX</td>
<td>&gt; 20 yr</td>
<td>5yr overall survival probability: 26% 27% with systemic metastasis</td>
</tr>
<tr>
<td>Carrie</td>
<td>156</td>
<td>n = 154 CSI (35/55Gy)</td>
<td>n=75 of 156 8in1; SIOP; Ifosf./CDDP/VCR</td>
<td>&gt; 18 yr</td>
<td>EFS 5yr=61% /10y=48% TTP: 30 mo Incidence: 0.5/million/year No significant benefit of chemotherapy</td>
</tr>
<tr>
<td>Peterson</td>
<td>45</td>
<td>CSI</td>
<td>ChX</td>
<td>&gt; 15 yr</td>
<td>50% recurred 10-76 months after initial treatment</td>
</tr>
<tr>
<td>Prados</td>
<td>47</td>
<td>CSI (all pat.)</td>
<td>ChX (32 of 47)</td>
<td>&gt; 15 yr</td>
<td>OS at 5 years: 81% (low risk) vs. 58% (high risk) p=0.03 DFS at 5 years: 54% (low risk) vs. 38% (high risk) p=0.05</td>
</tr>
</tbody>
</table>
In addition, the impact of chemotherapy in high-risk patients is unknown, especially in terms of whether intensive regimes are able to improve the well-recognised poor outcome. In a large French retrospective analysis the 5 and 10 year overall survival rates for patients without additional chemotherapy were 57 and 43%, respectively compared to 66% and 52% with chemotherapy; these differences were not statistically significant on a type 3 level of evidence (Carrie 1994). In Padova, 36 adult patients with standard or high-risk medulloblastoma were treated prospectively with a protocol consisting of pre-irradiation chemotherapy (cisplatin, etoposide, ifosfamide) followed by standard dose radiotherapy. The median time to progression was 81 months and the 5-year event-free and overall survival rates were 65.4% and 75.3%, respectively (Brandes 2003). Patients with a high-risk profile receiving additional chemotherapy achieved a 5-year progression-free survival of 61%. In Germany, 56 patients were analyzed who received additional chemotherapy according to the German HIT '91 protocol. Patients treated according to the protocol achieved a 5-year event-free survival of 67% as compared to 48% in...
those patients treated without strict adherence to the protocol guidelines. The outcome for all patients was 59%. Sixteen patients who received maintenance chemotherapy had a 5-year progression free survival of 78% as compared to 62% for 20 patients receiving sandwich chemotherapy. In M3 disease the outcome appeared worse (54%) than in M0 disease (71%) (Kühl, Rutkowski, personal communication). In adults, maintenance chemotherapy, however appears to be difficult to apply due to increased toxicities on a type 3 level of evidence (Greenberg 2001). However, the updated data from Brandes et al., after a median follow up of 7.6 years showed that the risk of recurrence appeared to increase markedly after 7 years of follow-up in low-risk patients. In the same analysis the authors showed that low-risk patients treated with radiotherapy alone and high-risk patients treated with radiotherapy and chemotherapy (upfront and adjuvant) did not differ significantly in terms of PFS or OS, raising the issue of a role for chemotherapy in low-risk patients (Brandes 2007). Furthermore, retrospective data from Padovani et al, with a consistent follow up suggested that in the standard-risk subgroup of patients there was no overall survival difference between patients treated with axial doses of > 34 Gy and patients treated with craniospinal doses < 34 Gy plus chemotherapy.

6.5 Chemotherapy in high-risk medulloblastoma

Metastatic disease, as described by Chang's classification (Chang 1969) (see Figure 5), seems to be a rare condition in adults as opposed to the situation in children. For example, in one French series medullary metastases were detected in 4 to 6% of cases, and positive cerebrospinal fluid (CSF) was found in 6-7% of cases. The positive CSF did not appear to be of prognostic significance, with a 10 year overall survival of 33% as compared to 59% in CSF negative patients. Spinal involvement had an important prognostic influence. The 10 year overall survival was 24% in patients with spinal metastases, compared to 58% in patients without metastatic deposits. The poor outcome, in spite of chemotherapy in intensive regimens, is well known in children, on a type 2 level of evidence. In the early CCSG trial published by Evans et al. the overall outcome for patients with M1-M3 disease was 5-year event free survival of 36% compared to 59% for patients with M0 disease (Evans 1990). In this study the effect of additional chemotherapy given in a maintenance regimen achieved a striking improvement with 5-year event-free survival of 46% compared to 0% for patients treated with radiotherapy alone. In the HIT '91 study the 3 year progression-free survival for patients with M2/M3-disease after radiotherapy followed by maintenance chemotherapy was 30%, compared to 83% for patients without metastatic disease, on a type 2 level of evidence (Kortmann 2000). There was no significant difference between outcome in the patients receiving sandwich chemotherapy or maintenance chemotherapy. A similar efficacy of additional chemotherapy appears to occur in adult patients on a type 3 level of evidence. In one series no patients survived after postoperative radiotherapy alone (Frost 1995). In the series of Chan, additional chemotherapy yielded a 5-year progression-free survival rate of 47% on a type 3 level of evidence (Chan 2000). Prados achieved a 5-year disease-free survival rate of 38% when additional chemotherapy was given on a type 3 level of evidence. Brandes et al. achieved a year progression-free survival rate of 45% in patients with M+ disease on a type 3 level of evidence. In the HIT study patients with M3 disease had a 5-year progression-free survival rate of 45% (Kühl, Rutkowski, personal communication). Because of the heterogeneity of patients and protocols no recommendations can be made yet with respect to a preferred regimen. Presently there is no evidence that more intensive chemotherapeutic approaches would result in a better outcome. Children with high-risk medulloblastoma are currently under investigation in phase II trials. Table 3: Medulloblastoma in adults: treatment outcome in retrospective studies on a type 3 level of evidence.

6.6 General recommendations for the management of medulloblastoma

Present treatment recommendations for the management of medulloblastoma are essentially based on experience in children. Prospective trials are lacking, but retrospective data indicate that irradiation of the craniospinal axis followed by a boost to the posterior fossa, with appropriate conventional doses as used in the paediatric population, is necessary for an optimal treatment outcome. The prognostic factors in adults appear to be similar to those in children, but differences such as tumour location and histological subtypes suggest the presence of specific biological properties which might have an additional influence. Controversy exists about the advantages of additional chemotherapy in
standard-risk patients. A major point of concern is the acute toxicity of chemotherapy given after radiation therapy. In the paediatric population, modification of chemotherapy was necessary in up to 60% of cases. Although the experiences for young adults were very promising in Germany the feasibility in older patients and in a larger cohort is largely unknown. It is known from diseases other than medulloblastoma that the tolerance of chemotherapy gradually decreases with increasing age. It is therefore essential that chemotherapy is investigated within a phase II-study in order to assess acute toxicity and feasibility. The EORTC BTG has established a working group for rare tumours of the CNS. **Recommendations for patients not included in controlled trials:**

- **Standard risk profile**
  The standard recommendation is surgery followed by immediate radiotherapy (craniospinal irradiation followed by a boost to the entire posterior fossa) using conventional doses (without dose reductions). Additional chemotherapy cannot be recommended since the benefit and possible toxicities are unknown.

- **High risk profile**
  For this, fortunately, rare subgroup of patients it is impossible to establish detailed treatment recommendations. As in children, conventional treatment schedules are associated with a poor outcome, consequently novel approaches are required. It is therefore recommended that these rare cases are discussed on an individual basis with a medical oncologist, radio-oncologist, and/or paediatric oncologist and that national medulloblastoma working groups are contacted. Data from the prospective trial by Brandes et al. suggested that upfront chemotherapy followed by radiotherapy is feasible, and provides long-term outcomes similar to that obtained with radiotherapy alone in standard risk patients ([Brandes 2007](#)).

6.7 The management of supratentorial primitive neuroectodermal tumours (stPNET)

In the paediatric population, treatment strategies are essentially based on those currently recommended for medulloblastoma. However, the long-term prognosis is considerably worse than in medulloblastoma. Craniospinal axis irradiation followed by a boost to the primary tumour site with sufficient dose is a prerequisite for optimal treatment outcome. The role of chemotherapy is uncertain and has never been tested in a randomised setting. Local tumour control is a point of major concern as the vast majority of tumours fail locally. In general, the disappointing results require intensification of treatment especially at the primary tumour site. Hyperfractionated radiotherapy, as in medulloblastoma, followed by local dose escalation to improve local tumour control is currently under investigation in the German HIT 2000 protocol. Hyperfractionated, accelerated radiotherapy is currently under investigation in prospective Italian and British studies.

**Adults**

As this tumour is very rare in adults and no data exist regarding optimal treatment. Further investigations are warranted with respect to local tumour control, the use of chemotherapy and the necessity for craniospinal irradiation. Additionally, biological and molecular genetic investigations are necessary to elucidate their pathobiological behaviour in comparison with childhood tumours and both adult and childhood medulloblastomas. As a general rule, the patients should be treated according to paediatric protocols. It is therefore recommended that these rare cases are discussed on an individual basis with a medical and/or paediatric oncologist and a radio-oncologist. National working groups should also be contacted.

7. LATE SEQUELAE

7.1 Long term sequelae

Cognitive and focal neurological deficits may have a great impact on long term survivors of brain tumors, regardless of the histology and grade of the tumors. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect even in those patients who appear to have a Karnofsky performance status of 100. Surgery in the so called silent areas may contribute to cognitive deficits. Less
clear are the late effects of radiation therapy on cognitive function. Radiotherapy is known to cause an early somnolence syndrome but may also cause late sequelae, in particular a delayed leukoencephalopathy with cognitive dysfunction and radiation necrosis (Corn 1994; Crossen 1994; Kumar 2000). In individual patients it is difficult however to entangle the direct effects of the tumor on cognition from late effects of treatment. A recent survey on cognitive deficits in progression free survivors of low grade glioma failed to confirm the generally assumed relation between radiotherapy and cognitive deficits (Klein 2002). Only in those patients who had been treated with fraction of more than 2 Gy evidence of increased cognitive dysfunction was observed. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies have suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, but today involved field radiotherapy is standard practice (Gregor 1996). Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction even in case of tumors distant from the hypothalamus-pituitary region (Brandes 2000). Apart cognitive deficits a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy. A risk of radionecrosis up to 5% in 5 years may occur after 60 Gy to one third or 50 Gy to two thirds of the brain volume or with 50-53 Gy to brain stem. Similar risk for blindness with 50 Gy to the optic chiasm. Also chemotherapy may induce late sequelae such as lymphoma or leukemia or solid tumors, lung fibrosis, infertility, renal failure, and neurotoxicity.

8. FOLLOW-UP

No general guidelines for the follow-up can be given, these should be tailored to the individual patient taking tumor grade, previous and remaining treatment options into account. To provide some rough guidelines, brain MRI may be repeated every 3 months and spinal MRI may be repeated every 6 months in standard risk, for the first 2 years; both may be then repeated every 6 months up to 5 years, and then performed annually. In high-risk medulloblastomas a brain and spinal MRI may be performed every 3 months for the first 2 years, as MRI would provide a more sensitive check during follow-up than waiting until signs develop, and then every 6 months. Obviously, unexpectedly new signs or symptoms may also call for imaging or a restaging of the patient.

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