CORRELATION OF TUMOUR VOLUME OF CHILDHOOD POSTERIOR FOSSA TUMOURS WITH OUTCOME

by

DIMITRIOS KOMBOGIORGAS, MRCS Ed

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Department of Clinical Neurosciences

School of Medicine

The University of Birmingham

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Abstract

Aim: To study if the amount of residual medulloblastoma correlates with improved survival.

Material and Methods: Tumour volumes were measured on preoperative and immediate postoperative MR scans of 37 children operated on for medulloblastoma between 1999 and 2006. The residuum ratio (post-/ preoperative tumour volume) was calculated and correlated to mortality and actuarial survival.

Results: Mean preoperative volume was 32 cm³ (range: 4.43-71.99 cm³, median: 30.61 cm³). Mean postoperative volume was 3.3 cm³ (range: 0- 23.3 cm³, median: 0.99 cm³). Mean residuum ratio was 10.7% (range: 0-74%); 28 (75.7%) patients had ≤15% residuum. At mean follow-up of 45 months (range: 6-117), 15 (40.5%) patients had died. Using either the presence of any residual tumour or a limit of 15% residuum ratio, there was no statistically significant difference in mortality or actuarial 5-year survival (p: 0.27, log rank). Also, the difference in 5-year survival of patients with a residual tumour > and ≤1.5 cm³ was not statistically significant (log rank, p= 0.367).

Conclusions: While there is a trend for patients with less residual medulloblastoma volume to have better outcome than those with more residual medulloblastoma volume, the number of the patients of this pilot study was not large enough to reach a conclusion and a larger study is required.

To my Wife

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List of abbreviations

ASPN: American Society of Paediatric Neurosurgeons

AUC: Area under the plasma concentration versus time curve

CNS: Central Nervous System

CSF: Cerebrospinal fluid

Cum Survival: Cumulative Survival

DICOM: Digital Imaging and Communications in Medicine

H&E: Haematoxylin and Eosin

FLAIR: Fluid Attenuated Inversion Recovery

IGR: Institute Gustave-Roussy

MRS: Magnetic Resonance Spectroscopy

MYBL2: V-mmyb avian myeloblastosis viral oncogene homologue-like 2

PBSC: Peripheral Blood Stem Cell

PET: Positron Emission Tomography

PNET: Primitive neuroectodermal tumour

PFS: Progression-Free Survival

SPECT: Single Photon Emission Computed Tomography

T1W: T1 weighted

T2W: T2 weighted

WHO: World Health Organization

Chapter 1

1. Introduction

1.1. Historical review

The term medulloblastoma was originally introduced in medical terminology by Bailey and Cushing in 1925 (1). They used this term to describe "a very cellular tumour of a peculiar kind, apparently arising over the roof of the fourth ventricle and projecting into the centre of the cerebellum" (1). The tumour tended to involve the fourth ventricle, displayed rapid growth and had an extremely bad prognosis. Historically tumours of this histological type had been referred by pathologists by various other names including neurocytoma, neuroblastoma and sarcoma (2-5).

Cushing had originally termed this tumour "spongioblastoma cerebelli" (5). They had followed Ribbert (6), unaware at the time of preparing their paper that Strauss and Globus (7) had previously and independently of Ribbert (6) employed the same term. After discussion between themselves, Bailey and Cushing adopted the term *Medulloblastoma* (1). They preferred this term because it indicates that the cells represent an embryonic stage earlier than either the spongioblast or neuroblast, a stage corresponding to the medulloblasts (8).

The terminology and the classification of medulloblastoma remained unchanged until 1983 when Rorke (9), Becker and Hinton (10) suggested that all malignant small cell tumours of central nervous system, including medulloblastoma, be classified as primitive neuroectodermal tumours (PNET) and be subdivided by location (11).

1.2. Epidemiology

Medulloblastoma is the commonest type of malignant brain tumour of childhood and the second most common overall after astrocytomas (12). It constitutes approximately 20% of childhood cerebellar tumours with a male to female ratio that ranges from 1.5:1 to 2:1 (12-16).

The overall incidence among children aged 0 to 19 years is 0.63 per 100,000 person-years or 16% of all paediatric brain tumours in the United States (11;12). In childhood the tumour has a bimodal age distribution, with peaks at 3 to 4 years and at 8 to 9 years (11;16;17). Medulloblastoma in adults is rare, accounting for only 1% of all CNS tumours. The incidence is highest between the age of 20 to 34 years at 0.21 per 100,000 person-years and reduces to 0.05 per 100,000 person-years between 55 to 64 years before dropping to zero after the age of 64 years (18;19).

In their series Chang et al reported that about 55% of tumours originate from the vermis, 25% from the cerebellar hemisphere, 3% from the brain stem, and an undetermined origin in 17% (20).

1.3. Cell origin

Medulloblastoma is believed to be derived from the granule-cell progenitors which are located in the external granular layer of the cerebellum (21-24). This is a germinal zone harbouring actively proliferating progenitor cells originating from the rhombic lip during embryonic development (24). The external granular layer eventually disappears as all cell division ceases and all post mitotic neurons move to the internal granular layer (25).

1.4. Modern Histopathological Classification

Embryonal (primitive) neuroepithelial neoplasm features include:

1) Predominance in children

2) Tendency to disseminate through cerebrospinal fluid pathways

3) Dominant population of small undifferentiated cells

4) High mitotic indices and widespread apoptosis

5) Potential for divergent neuroepithelial differentiation (26).

In 1983, Rorke (9) and Becker and Hinton (10) noted the histological similarity of medulloblastomas and PNETs. They appear as small, round, blue-cell tumours with hyperchromatic nuclei, minimal cytoplasm, and various degrees of calcification on haematoxylin-eosin stain (Figure 1) (27). Microvascular proliferation is relatively uncommon (28).

Histologically, childhood and adult medulloblastoma are identical. They are highly cellular, malignant invasive tumours corresponding to WHO malignancy grade IV (29).
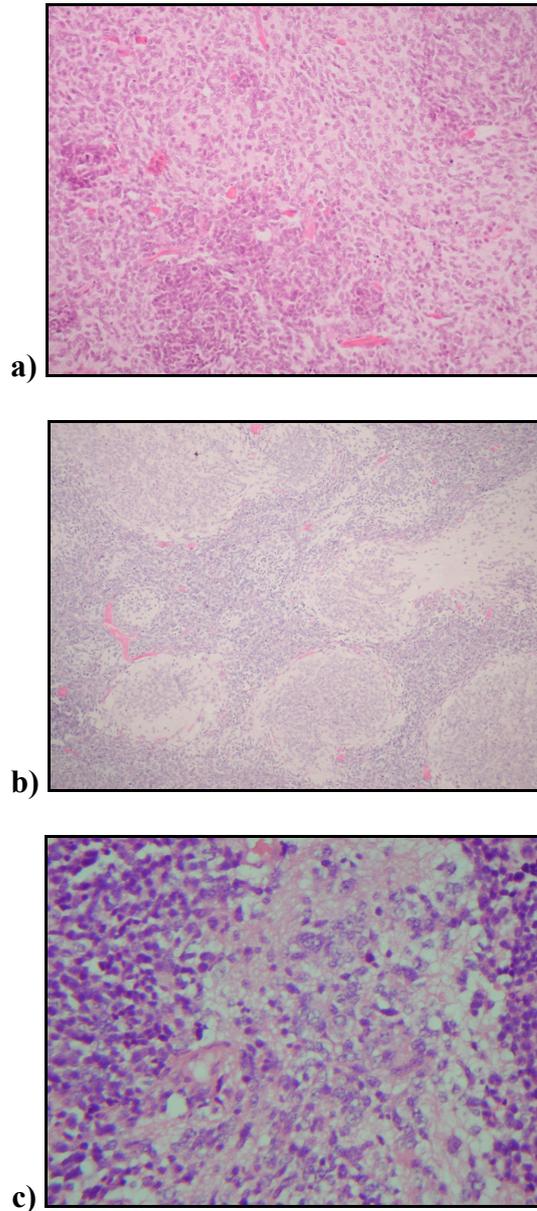
Figure 1: Histological features of medulloblastoma: **A.** Classic medulloblastoma: sheets of densely packed cells with round to oval shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Cells stained with haematoxylin and eosin. **B.** Desmoplastic medulloblastoma is characterised by nodular reticulin-free zones ("pale islands") surrounded by densely packed, highly proliferative cells, which produce a dense intercellular reticulin fibres network. Cells stained with reticulin. **C.** Large cell - Anaplastic medulloblastoma: marked nuclear pleomorphism, cell-cell wrapping and high mitotic activity. Cells stained with haematoxylin and eosin. Photographs courtesy *of* Dr Marie-Ann Brundler Consultant Pathologist, Birmingham Children's Hospital, U.K.

Based on WHO classification of tumours of the Nervous System (2002), the Embryonal Tumours group includes the following types of tumours (29):

Medulloepithelioma 9501/3

Ependymoblastoma 9392/3

Medulloblastoma 9470/3

    Desmoplastic Medulloblastoma 9471/3

    Large cell Medulloblastoma 9474/3

    Medullomyoblastoma 9472/3

    Melanotic Medulloblastoma 9470/3

Supratentorial primitive neuroectodermal tumour 9473/3

    Neuroblastoma 9500/3

    Ganglioneuroblastoma 9490/3

Atypical teratoid / rhabdoid tumour 9508/3

Macroscopically medulloblastomas are pink or purple coloured tumours. They are poorly demarcated with a soft and friable consistency. The tumour may extend through the fourth ventricle into the cerebral aqueduct or into the cisterna magna via the foramen of Magendie (11). It may invade the cerebellum, brainstem, or cerebellar peduncle. Involvement of the cerebellar hemispheres is uncommon in children but is more frequent in adults (11). Brainstem infiltration occurs in 15% to 36% of cases (11;30). There may be

foci of haemorrhage but cysts are unusual. Areas of necrosis may occur but are not extensive (11).

Microscopically, differentiated medulloblastomas with neuroblastic features are distinguished by Homer Wright rosettes (31). These rosettes are formed by cells surrounding fibrillary structures and characteristically do not encircle blood vessels (32). Rarely, the tumour grows extra-axially along the cerebellar surface without invading adjacent parenchyma (33). Mitoses and apoptotic bodies are plentiful in regions where the nuclear to cytoplasmic ratio is high (26).

The desmoplastic variant of medulloblastoma is characterized by distinctive reticulin-free "islands" of densely packed monomorphic round cells among the reticulin-rich area. It is seen in up to 50% of adult cases of medulloblastoma compared to 15% in children (33;41). It has a tendency to be located within the cerebellar hemisphere and is often firmer in consistency and is better demarcated than the classical medulloblastoma as a result of the greater connective tissue component of the tumour (34).

Neuronal differentiation is often prominent in nodular medulloblastomas. Focal melanin production and evidence of striated muscle differentiation can both occur in medulloblastomas creating the variants melanotic medulloblastoma and medullomyoblastoma respectively. Nodular

medulloblastomas contain centres of dark cells surrounding pale islands, analogous to the germinal centers of a lymph node. They are associated with a better prognosis compared to that of the classic histological subtypes in children (35-37), but the reverse is true in adults (38).

Large-cell medulloblastoma is another variant of medulloblastoma and has a poor prognosis (26). It has recently been characterised as a highly malignant variant, which represents about 4% of medulloblastomas (39). Only a few cases have been reported in the literature. All patients were male and the age of manifestation ranged from 13 months to 4 years (29). Morphologically this variant resembles the atypical teratoid / rhabdoid tumours of the cerebellar region, but differs on the basis of its immunophenotype and cytogenetic features (29).

1.5. Staging

Medulloblastoma has a strong propensity to metastasize within the subarachnoid space due to its tendency to penetrate the ependymal surface (28). Metastases may form microscopic deposits, gross nodules, or en plaque masses along the brain or spinal cord. An autopsy series revealed that cerebrospinal spread occurs in up to 50% of patients (26;40). Extraneural

metastasis occurs in approximately 5% of patients and most commonly involves the bone marrow (11).

In 1969, Chang et al developed an internationally recognised *operative* staging system for patients with medulloblastoma as clinical staging was deemed inaccurate (20). That system was developed with the International TNM-staging designation. Since there are no lymphatic channels in the brain, they omitted the letter N in their staging system. Their proposed operative staging system for cerebellar medulloblastoma is outlined in Table 1 (20).

In 1985, Laurent et al reported a postoperative MAPS (metastasis, age, pathology, surgery) classification system (41). The primary purpose of the MAPS system was to evaluate the prognostic impact of the extent and degree of tumour burden after initial definitive surgery, and to analyze this data in a prospective manner. They noted the importance of obtaining enhanced CT scans of the brain postoperatively in order to visualize the extent of residual tumour as well as intracranial metastasis. They recommended CSF analysis (cells, polyamines), CT-myelogram, bone scan, leptomeningeal / bone biopsy and CT - metrizimide myelography after surgery, aiming to detect distal metastasis (Table 2) (41).

CSF cytology is performed using CSF drained via lumbar puncture because this method is more sensitive than the use of ventricular CSF for detecting

disseminated disease (42). Lumbar puncture prior to surgical resection presents an unacceptable risk of cerebral herniation and should be performed after tumour has been resected. However, it should not be performed any sooner than 2 weeks postoperatively in order to avoid false positive cytology results caused by the liberation of tumour cells during surgery (18;43).

In Chang's classification (41) the "T" represented the location and size of the tumour (20). This was a staging system based on preoperative and intraoperative findings and was not related to the postoperative findings. This led to confusion in both staging and treatment of these tumours.

Aiming to alleviate this problem, Laurent et al added a surgical "S" component in their classification that must be confirmed by a postoperative enhanced CT scan of the brain. Stage S3 related to invasion of the brain stem structures including the mesencephalon and/or the diencephalon, and/or myeloencephalon by the tumour. It remains unclear as to the reason why they selected a residual tumour diameter of 1.5 cm as the size to distinguish the stage S1 from stage S2 on postoperative CT scan (41).

Table 1. Chang Staging System (20)

T 1: Tumour less than 3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres.

T 2: Tumour more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle.

T3: It was subdivided into:

T 3a: Tumour further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus.

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

T 4: Tumour further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumour extending to the upper cervical cord.

M 0: No evidence of gross subarachnoid or haematogenous metastasis.

M 1: Microscopic tumour cells found in lumbar cerebrospinal fluid.

M 2: Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles

M 3: Gross nodular seeding in the spinal subarachnoid space

M 4: Extraneuroaxonal metastasis.

Table 2. MAPS Classification System (41)

Metastasis (M)

M0: No evidence of metastasis

M1: Cells present in leptomeninges or cerebrospinal fluid

M2: Nodular seeding demonstrated in the supratentorial compartment
(enhanced CT scan)

M3: Nodular seeding of the spinal compartment (myelogram)

M4: Combined nodular seeding of two compartments (supratentorial and/or infratentorial
and/or spinal)

M5: Evidence of systemic seeding (bone marrow, various bone and viscera scans)

Age (A)

A1: >3 years

A2: <3 years

Pathology (P)

P1: Microscopic appearance: Benign, classic for tumour type, well-differentiated single
cell line

P2: Microscopic appearance: Anaplastic, malignant, multiple differentiated cell lines

Surgery (S)

Postoperative *residual tumour* was confirmed by *enhanced CT* scan of the brain

S0: No tumour

S1: Remaining tumour < 1.5 cm (largest diameter)

S2: Remaining tumour > 1.5 cm (largest diameter)

S3: Remaining tumour (any size) invading brain stem structures (medulla oblogata,
pons, midbrain, diencephalon)

S4: Remaining tumour (any size) extending into more than one central nervous system
compartment (supratentorial, infratentorial, spinal compartments)

1.6. Prognostic factors

The prognosis of patients with medulloblastoma depends on several factors (Table 3). These factors include the presence or absence of metastases at diagnosis (44-46), the radiotherapy modality used (45;47), the use of chemotherapy (48-51), the extent of the residual tumour (44;46;50;52-55), the patient's gender (50;54), the duration of the symptoms (56), whether a ventricular-peritoneal shunt is inserted within 30 days after the surgical resection of the tumour (47), [18F] fluorodeoxyglucose uptake during positron emission tomography (57) and the genetic and molecular profile of the medulloblastoma (44;58). A short duration of symptoms is associated with more advanced medulloblastoma (56). This finding has potentially significant implications for the identification of prognostic groups in medulloblastoma as well as medicolegal claims of "delay in diagnosis" (56). Dissemination of medulloblastoma at diagnosis remains one of the most important clinical predictors of outcome (18;59;60). Leptomeningeal metastases have been reported to occur in up to 46% of patients in different series but usually range from 10% to 35% of cases (61-63). Extra-axial metastases are uncommon at initial presentation. Approximately 5% of patients with medulloblastoma may be expected to develop systemic metastases (61;64). Extracranial sites of spread include the bone, bone marrow, liver, lungs and lymph nodes and are usually associated with end stage disease (18;65-67). Rare sites of extracranial

metastases which have been anecdotally reported in the literature include breast (68) and fibroadenoma of the breast (69).

The importance of the role of surgery in patients with medulloblastoma is widely recognised. It reduces the volume of tumour, alleviates brain stem compression from the tumour and restores the patency of CSF pathways by relieving CSF obstruction at the level of the fourth ventricle.

Jenkin et al reported that total tumour resection as determined by the surgeon, was the most significant favourable prognostic factor. They also noted that residual tumour was demonstrable on 54% of post-operative scans and was associated with a significantly poorer outcome (70). In contrast, Bourne et al reported that the extent of surgical resection as estimated by the neurosurgeon, did not significantly influence prognosis. However, they also found that the presence of residual contrast enhancement seen on CT scans performed immediately postoperatively was associated with a significant decrease in the 5-year recurrence-free survival rate (71).

Albright et al studied a series of 203 children with medulloblastomas who were treated according to the Children's Cancer Group-921 protocol. After univariate analysis of data on the extent of primary medulloblastoma excision and the extent of the residual tumour, they found that there was no correlation between either of these factors as independent variables on progression free survival (Table 4) (52).

Table 3. Prognostic Factors Associated With Outcome for

Medulloblastoma (72)

Increased Survival	*Diminished Survival*
Sex, female (16;54)	Younger age (78)
Gross total resection (55)	Subtotal resection (55)
No metastasis (55)	Metastasis (55)
Desmoplastic histology (36)	Insertion of a ventricular-peritoneal
Increased apoptosis index (73)	shunt within 30 days after the surgical
Hyperdiploidy (74)	resection of the tumour (47)
High TrkC expression (75-77)	[18F] fluorodeoxyglucose uptake during
Radiotherapy (45;47), Chemotherapy (48-51)	positron emission tomography (57)
Long duration of the symptoms (56)	Large-cell anaplastic histology (39;79)
	Elevated Ki-67 / MIB-1 proliferative
	index (80)
	Aneuploidy (81)
	Elevated ErbB2 expression (44;58)
	Isolated 17p loss of heterozygosity (44;82)
	Elevated expression and amplification of
	c-MYC (83-85)
	Over-expression of calbindin-D28k (86)
	Expression of genes related to cell
	proliferation and metabolism: (MYBL2)
	enolase 1, LDH, HMG1(Y), cytochrome
	C oxidase and multidrug resistance
	(sorcin) (77;87)

Table 4. Extent of Medulloblastoma Resection (52)

Total   No visible tumour evident at the completion of resection

Near-total   >90% resection, but visible tumour remains

Subtotal   51-90% resection

Partial   11-50% resection

Biopsy   ≤ 10% resection

However, on multivariate analysis the extent of the residual tumour was found to be an important prognostic factor determining outcome in certain children. In particular, the extent of residual tumour did correlate with better prognosis in children with:

1) No disseminated disease (M0) and <1.5 cm² of residual tumour on immediate post-operative CT scan of the brain, and

2) Age more than 3 years with no disseminated disease (M0) at the time of diagnosis and with residual tumour <1.5 cm² on immediate post-operative CT scan of the brain (52). In that case, the residual tumour was an important variable in outcome and one that neurosurgeons can control.

A residual tumour of less than 1.5 cm² is statistically associated with improved survival but only in the subset of patients aged 3 years or older in whom CT / MRI scanning confirmed M0 disease at diagnosis (3).

The question thus arises of why CT / MRI scan - detectable disease would be related to survival, whilst the neurosurgeons' observations would not? The absolute residual tumour burden, which is most likely to be in the range of 1 billion cells (1 cm³), is the determining factor for the efficacy of chemotherapy and radiotherapy rather than the percentage of tumour removed.

Zeltzer et al reported that the progression free survival distributions at 5 years for patients with non-metastatic disease and <1.5 cm² of residual tumour on the immediate postoperative CT / MRI scan (within six days after the primary operation), versus ≥1.5 cm² of residual tumour by scan, were significantly different (p= 0.023; 78%+/-6% v 54%+/-11%, respectively) (55). There is however no clear rationale behind the selection of 1.5 cm² as a cut off point for the size of residual tumour on immediate postoperative CT or MRI scans of the brain.

The significance of total medulloblastoma excision was demonstrated in the SFOP trial for young children (less than 5 years of age) with non-metastatic disease (88). In that trial, it was shown that cure was possible with conventional chemotherapy alone in children with non-metastatic medulloblastoma who underwent gross total resection confirmed by early radiological assessment, but is not sufficient in isolation for treatment of those with metastatic or incompletely resected medulloblastoma (88).

In the BBSFOP protocol, children who had no postoperative radiological residual disease and no metastasis had a 73% 5-year survival, and most children did not receive craniospinal radiotherapy (88). These findings are consistent with those of the HIT-SKK study (89). Furthermore, an update of the Baby Paediatric Oncology Group I study (90) reported a 69% 5-year

overall survival in the same group of patients, although most patients received craniospinal radiotherapy (but at reduced dose of 24 Gy).

These results suggest that a future strategy to improve survival of children with medulloblastoma should include full staging with both pre- and post-operative MRI scanning of CNS (52;55;91) so as to offer tailored neurosurgical treatment with maximal tumour cytoreduction when possible (55).

1.7. Risk Stratification

Currently, children with medulloblastoma are divided into two groups according to risk for recurrence, an *average-risk* group and a *high-risk* group. This division is based on three *clinical prognostic factors*: age, extent of tumour resection and metastatic disease (92).

Children younger than 3 years of age have markedly poorer outcomes. The reasons for this may relate to the biology of tumours arising early in life or may be due to associations with known prognostic indicators (18) such as:

1) Younger children (less than 5 years of age) more commonly present with metastatic disease (62).

2) Oncologists may be reluctant to use conventional doses of craniospinal radiotherapy (93).

3) Young children more commonly have subtotal tumour resections (94).

Residual tumour is assessed by postoperative MRI scanning within 48 to 72 hours in order to limit the impact of postsurgical changes on MRI scan interpretation (52)

Clinically, patients are divided into M0 and M + (M 1 - M4) groups for risk stratification. The survival disadvantage suffered by patients with metastatic disease is illustrated by Packer et al in a large multi-institution, single-armed study treating children with radiation and chemotherapy consisting of lomustine, cisplatin, and vincristine. Patients with M + disease at the time of diagnosis were shown to have a poorer 5 year progression free survival (67% ± 15%) compared to those without metastatic disease (90%, ± 6%, p= 0.037) (49). Although M1 disease trends toward poorer outcomes, it has not been demonstrated to confer a statistically significant increased risk of treatment failure in the largest studies (55;95;96). With the exception of M1 however, the M stage continues to be the most robust clinical prognostic indicator used in the current scheme of risk stratification (18).

Molecular biology also provides increasing insight into the genetic events that lead to the formation of medulloblastoma, as well as the molecular characteristics that predict a poor response to current therapeutic regimes. Discussions on this topic often contain three risk categories: high, intermediate and average. The intermediate risk category for example, could contain patients with brainstem invasion, Ml disease, age less than 3 but elevated TrkC, or patients with a subtotal tumour resection (18;43).

In view of the absence of an accurate assessment of disease risk among children with medulloblastoma, Gilbertson et al (44) studied 41 primary medulloblastoma cases aiming to establish whether molecular abnormalities provide prognostic information for patients with medulloblastoma in addition to that afforded by clinical risk stratification. Patients' tumour samples were analysed for ErbB2 receptor expression using immunohistochemistry, and for aberrations of chromosome 17 and amplification of the MYC oncogene using fluorescence in situ hybridisation (FISH). ErbB2 (also known as HER2/neu) abbreviates "Human Epidermal growth factor Receptor 2" and is a protein associated with more aggressive behavior in some breast cancers. It is a cell membrane surface-bound tyrosine kinase receptor and is normally involved in the signal transduction pathways leading to cell growth and differentiation. HER2 is thought to be an orphan receptor, with none of the EGF family of ligands is able to activate it. However, ErbB receptors dimerise on ligand binding, and HER2 is the preferential dimerisation partner of other members

of the ErbB family (97). The HER2 gene is a proto-oncogene located on the long arm of human chromosome 17(17q21-q22) (98).

Gilbertson et al found that the ErbB2 receptor and deletion of 17p were detected in 80% and 49% of medulloblastomas respectively. In addition, 17p loss occurred either in isolation (20%), or in association with gain of 17q (29%), compatible with an isochromosome of 17q. Amplification of MYC was detected in only 2 tumours. MYC [v-myc myelocytomatosis viral oncogene homolog] protein is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. It functions as a transcription factor that regulates transcription of specific target genes. Mutations, over-expression, rearrangement and translocation of MYC gene have been associated with a variety of hematopoietic tumors, leukemias and lymphomas, including Burkitt 's lymphoma (44).

Importantly, this study revealed no significant relationship between patient age and any molecular abnormality (44). High molecular risk patients were designated as those with high ErbB2 receptor expression and / or isolated 17p loss, while low molecular risk patients were designated as patients whose tumours demonstrated neither aberration. Combined analysis of clinical and

Molecular factors enabled more accurate prediction of disease risk than clinical factors alone, identifying a sub-population of patients with particularly

favourable disease outcome (44). A high ErbB2 oncogene protein expression was defined as presence of ErbB2 oncogene protein in ≥50% of tumour cells. FISH was employed to identify both the abnormalities of chromosome 17 (imbalance on the short and long arms of chromosome 17) and MYC oncogene amplification in material derived from each of the tumour blocks employed in the analysis of ErbB2 receptor expression.

More recently, Crawford et al reported a generalised algorithm for the stratification and treatment of medulloblastoma on the basis of age and risk stratification, highlighting the possibility that the presence or absence of biological tumour markers may alter risk stratification and future treatment options (Figure 2) (99). Whether these markers (genes encoding neurotrophin-3 receptor, MYC, ErbB2, β-catenin, survivin, p53) are useful to further refine the clinically based stratification or obviate the need for clinical staging is unclear. The incorporation of these markers into the risk stratification scheme might also result in the definition of more exact risk subset groups (99).

The most common site for a relapse is the posterior fossa in both children and adults (18). Late relapse is much more common in adults than in children, with adults displaying a median time to recurrence of 26 months and 29% of recurrences occurring more than 5 years after treatment (19). This is in contrast to the occurrence of 75% of paediatric relapses which occur within 2 years (18;100).
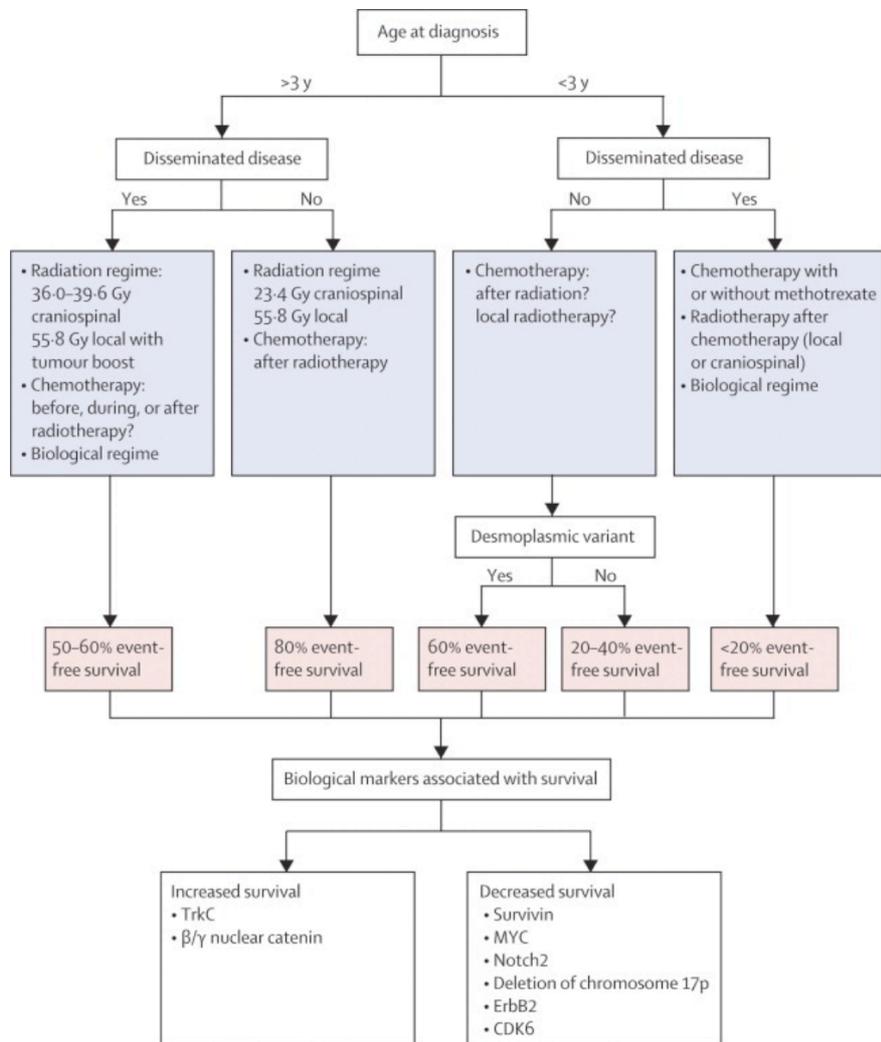
Figure 2: Treatment scheme for medulloblastoma (99)

Crawford et al. Lancet Neurology 2007;6: 1073-85.

1.8. Diagnosis

1.8.1. Clinical presentation

Children with medulloblastoma most commonly present with the classic symptoms of morning headache, vomiting, and lethargy, which are caused by a posterior fossa mass or associated hydrocephalus. Infants may have irritability and poor feeding. Cerebellar signs include trunkal ataxia, gait / limb ataxia or / and dysmetria. Brain stem invasion by the medulloblastoma may cause bulbar or facial nerve palsy. Sixth nerve palsy is usually as a result of hydrocephalus or intracranial hypertension. Impaction of the cerebellar tonsils into the foramen magnum may also cause torticollis (11). Affected children tend to maintain a fixed posture, with the head tilted and partially externally rotated to one side in order to reduce the pain caused from stretching and irritation of the dura. Passive flexion of the patient forward is actively resisted and results in severe pain (101). Diplopia is often present and is secondary to VIth cranial nerve palsy. Other symptoms include drowsiness, reduced appetite, loss of weight, blurred vision, macrocrania and behavioural changes (11;30;102).

Infants less often exhibit the classic triad of symptoms because of unfused sutures and corresponding compensation for the elevated intracranial pressure.

Common symptoms in infants include macrocephaly, a full anterior fontanel, irritability, intermittent vomiting and "sun-setting". Papilloedema, whilst very common in older children, is rare in infants (11;30;102).

Symptoms usually last from a few weeks up to three months (30), although cases of symptoms lasting for one year have been reported in the literature (103). A long duration of symptoms prior to diagnosis may correlate with a lower stage of tumour, whereas a shorter duration correlates with a higher stage of disease. A delay in diagnosis may be attributable to the clinicians' low index of suspicion of medulloblastoma as the causative factor of non-specific symptoms such as headache, nausea or vomiting. Patients with early morning headaches and vomiting may have undergone extensive gastrointestinal evaluation before the diagnosis of a brain tumour is finally made (102).

1.8.2. Clinical signs

The most common neurological signs at the time of presentation include: truncal ataxia, ataxic gait, nystagmus, cranial nerve palsy, papilloedema, increased head circumference, torticollis, limitation of upward gaze, and reduced visual acuity (11;30;102). In addition, increasing head circumference

and full anterior fontanel with widely split cranial sutures may be the presenting signs in an infant with raised intracranial pressure due to hydrocephalus (104). Extension of medulloblastoma into the cerebral aqueduct may result in fourth cranial nerve palsy due to direct compression of its nucleus and decussated fibres around the periaqueductal grey matter (104;105). Although leptomeningeal metastases are common in children with medulloblastoma (30), the presence of spinal intramedullary metastasis at diagnosis is very rare and only three cases have been reported in the literature to date (106-108).

1.8.3. Radiology

On an unenhanced CT, medulloblastoma appears as a homogeneous hyperdense and well-circumscribed mass seen in the midline associated with the vermis (109). Vermian medulloblastomas can extend into the contiguous cerebellar hemisphere, brain stem, fourth ventricle and rarely through the aqueduct into the third ventricle (109). Medulloblastomas arising in the fourth ventricle can extend through the foramina of Magendie and Luschka (110). Uncommonly, medulloblastoma can present as a solitory cerebellopontine angle tumour (110). In older children and adults medulloblastomas have a greater predilection for the cerebellar hemispheres. Cyst formation occurs in

10% to 20% of paediatric cases and 59% to 82% of adult cases (111). Haemorrhage occurs uncommonly in paediatric medulloblastomas (111) and the presence of calcifications in the tumour are rare (109;111).

MRI based measurements of medulloblastoma range from 2.5 cm to 5.0 cm (mean 4 cm) in transverse diameter on axial cuts (112). Medulloblastomas usually show moderate contrast uptake with a heterogeneous enhancement pattern (112). However, atypical features of homogenous or patchy enhancement may occur (113) Figure 3. On FLAIR sequences the signal is isointense to grey matter. This is in contrast to most other CNS tumours which tend to have signal that is more intense than grey matter (18).

Other imaging modalities such as MRS, PET and SPECT are also used in the management of patients with medulloblastoma, most commonly as a clinical aid to distinguish tumour recurrence from post-therapy necrosis. In medulloblastoma, MRS typically shows raised level of choline (a marker of biomembranes) and decreased level of N-acetyl aspartate (a neuronal cell marker) and other mobile lipids (114). Taurine level (usually raised in astrocytomas) is occasionally seen to have a reduced peak in medulloblastomas on MRS (115). PET with [18]flyorodeoxyglucose (FDG) uptake has been used to study medulloblastoma and a positive result is found to be inversely related to survival (57). SPECT has also been used to study medulloblastoma, particularly to differentiate post-radiation changes and

gliosis from tumour recurrence (116). Newer neuroimaging modalities such as diffusion tensor imaging have been used for preoperative and postoperative assessment of corticospinal tract invasion in various brain tumours (117). Changes in relative anisotropy as assessed by diffusion tensor imaging, have been associated specifically with poor intellectual outcome after treatment for medulloblastoma (99;118).

Metastatic deposits are typically identified on gadolinium TlW images as enhancing nodules or described as a "carpet-like" or "zuckerguss" (icing sugar) covering of the leptomeningeal surfaces of the brain and spinal cord. Drop metastases, which occur in up to 40% of patients, are most commonly seen in the lumbosacral and thoracic areas. However, these classic features on imaging as described above cannot always be distinguished from nerve root clumping or pial enhancement. It is therefore imperative to obtain an MRI of the whole spine before and after treatment for comparison (99). Problematically, non-enhancing metastatic disease can also be present. The non-enhancing metastases are often only identified on T2-weighted images as areas of distortion in the subarachnoid spaces or as areas of abnormal signal on FLAIR or diffusion images (18;119). MR is the superior study, but CT myelography may be more beneficial in specific cases for the detection and evaluation of drop metastasis on distal spinal nerve (111).

Early enhancement has been shown to be associated with residual tumour. Imaging of patients after the third postoperative day may be misleading as dural and operative bed enhancement may simulate metastatic subarachnoid and leptomeningeal metastatic disease (109). Enhancement after 3 days can be seen in either residual tumour or in foci of neovascularisation within the postoperative brain thus resulting in potential misinterpretation of CT or MR scans (109;120). Consequently, routine postoperative cranial imaging by MR should be obtained during the immediate postoperative period and certainly within the first 72 hours of primary medulloblastoma excision (121). Also the use of Surgicel for haemostasis in the tumour bed may also be misinterpreted as residual tumour on early post operative CT scan and should be taken into account when interpreting the scans (109) (Table 5).

Although, Roebuck et al could not prove that surveillance imaging improves survival in children with medulloblastoma, they found that it is effective in detecting potentially curable medulloblastoma relapses and should be offered to all patients (122). Currently, surveillance MR imaging of children with medulloblastoma is used routinely. MRI scan of the head and spine are performed at least every 3 months for the first year after surgery and then at least every 6 months until three years post treatment in order to assess the result of treatment and to diagnose asymptomatic relapse of the disease.
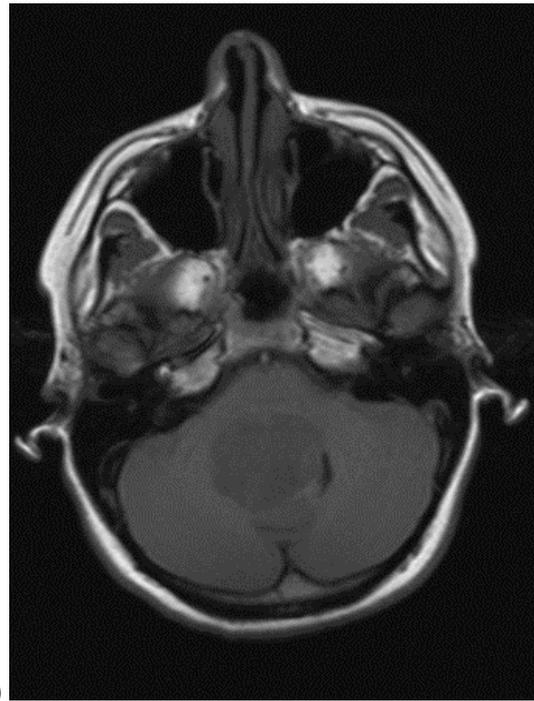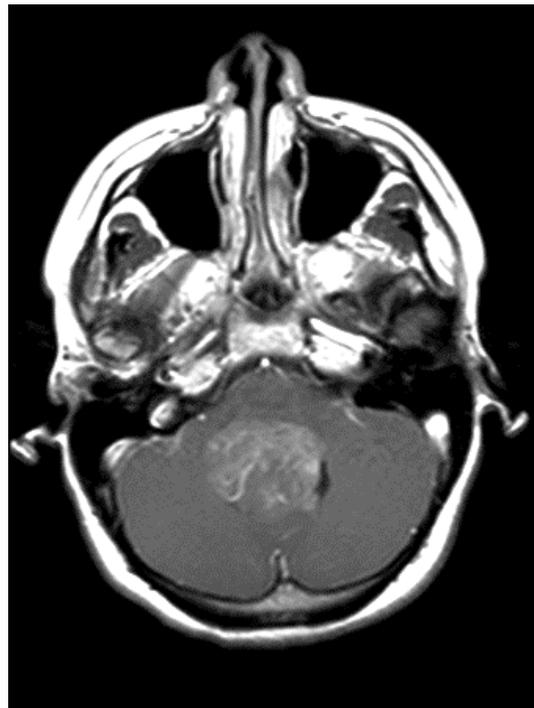
Figure 3. MRI Scan of medulloblastoma (a) prior to contrast,

(b) after contrast enhancement

Table 5. Radiological profile of Medulloblastoma (111)

Feature	Medulloblastoma
Unenhanced CT	Hyperdense
Enhancement	Moderate
Calcification	Uncommon (10%-21%)
Origin	Vermis
T2W	Intermediate intensity
Site	Midline
Subarachnoid seeding	15%-50%
Cyst formation	10-20%
Foraminal spread	No
Haemorrhage	Rare
MRS Metabolite	
NAA	Low
Lactate	Absent
Choline	High

1.9. Management

At present, the treatment of patients with medulloblastoma includes surgical excision of the tumour followed by radiotherapy and/or chemotherapy. For average risk patients with medulloblastoma, the current treatment regime includes maximum surgical resection followed by chemotherapy and whole neuroaxis radiotherapy (123). Recently in the USA and Europe, the standard neuroaxis radiation dose has been reduced from 36.0Gy to 23.4 Gy in an attempt to reduce the neurological toxic side effects which are still present, especially in children younger than 8 years of age (124).

1.9.1. Surgery

Surgical treatment for medulloblastoma has improved dramatically over the past thirty years. This is primarily related to fundamental innovations in surgery and technology including the use of diathermy and microscope, new surgical instruments and the CUSA device in conjunction with significant improvements in general anaesthesia and postoperative care.

The diagnosis of medulloblastoma is usually strongly suggested by the preoperative imaging studies. The T1W contrast-enhanced cranial MRI is carefully examined for evidence of nodular tumour deposits. An MRI

examination of the complete spine is obtained if the clinical condition of the child permits. An uncooperative child should not be subjected to deep sedation to obtain a detailed spinal study preoperatively since this may mask any deterioration in the neurologic condition and precipitate hypoventilation (125).

In the stable patient a preoperative MRI of the spine is desirable as it decreases the risk of obtaining false positive results for metastases created by the presence of blood in the thecal sac in the immediate postoperative period. In addition, prior knowledge of disseminated disease should restrain the surgeon from removing small tumours from critical locations which is associated with high risk of significant neurological complications (125).

1.9.1.1. Surgical complications

At the beginning of the last century the reported mortality rate following surgery for cerebellar tumours was 42% (104;125;126). Since then, the associated mortality of the surgical resection of medulloblastoma has steadily decreased. Cushing (127) in 1932 and Bailey (128) in 1939 (as stated by Sutton et al (125)) reported a mortality rate of 25.2% and 15.5%, respectively. Thirty eight years after Bailey's report, Bloom described an operative

mortality rate of 10% (100). Currently, the mortality rate ranges from 1% -
5% (27) ,(104;125).

The most common postoperative complications following posterior fossa
surgery for the resection of medulloblastomas include haematoma, infection /
meningitis, aseptic meningitis, hydrocephalus, pseudomeningocele, CSF leak,
cerebellar mutism, cranial nerve palsy, and hemiparesis (104;129-132). Spinal
deformity occurs in 5% of cases after a posterior fossa tumour resection (133).
It is typically seen within a year of surgery and is predisposed by laminectomy
of C2 or lower, local wound complications and possibly postoperative neck
weakness (133).

Brain stem damage may result in the need for nutritional and respiratory
support such as gastrostomy, tracheostomy, or prolonged ventilatory support.
"Pseudobulbar palsy" syndrome may occur approximately 72 hours following
surgery for midline posterior fossa tumours (125;134). It tends to resolve over
weeks and months and is attributed to retraction-induced oedema of the
cerebellar peduncles, upper pons and midbrain (125;134).

Cerebellar mutism is a well recognised complication following posterior fossa
surgery for cerebellar tumours (135-138). The reported incidence rate in
paediatric medulloblastoma patients varies widely between different studies
(131;139-142). More than 200 cases have been reported in the literature

(136;140;142). It usually develops during the first 3-4 postoperative days and may persist for several months (38;129;131;140). The deficit usually recovers over period of weeks to 6 months (125) but some patients may experience a permanent deficit.

Neuropsychological consequences of cerebellar tumour resection include expressive language deficits (37%), visual-spatial deficits (37%), both expressive language and visual-spatial deficits (16%) and fine motor coordination impairment (74%) (143).

1.9.2. Radiotherapy

The prognosis of patients with medulloblastoma has changed markedly since the introduction of postoperative irradiation of the whole neuroaxis; improving survival rates to 54% (144). Furthermore, the combination of surgery with radiotherapy and/or chemotherapy has improved the prognosis of children with medulloblastoma (145).

Until recently the therapeutic approach for standard risk medulloblastoma has consisted of complete or near complete surgical resection followed by post-operative craniospinal radiotherapy. The conventional doses of radiotherapy

are around 36 Gy to the craniospinal axis together with a boost of 18 to 20 Gy to the posterior fossa (total dose of 54 to 56 Gy) (146). In addition, conventional fractionation in radiotherapy has evolved empirically and generally involves giving one fraction per day, five days per week Monday to Friday. In paediatric radiotherapy practice, the daily dose per fraction is generally between 1.5 and. 2.0 Gy. 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. Exceeding the CNS tissue tolerance dose carries an increased risk of severe late morbidity including radiation necrosis (147). This limits the dose of radiotherapy that can be delivered for CNS tumours.

Hyperfractionated radiotherapy involves giving a smaller dose per fraction, with radiotherapy fractions administered at least twice each day. The aim of hyperfractionation is to improve the therapeutic ratio, either by enhancing the anti-tumour effect without an increase in late side effects, or by maintaining the same level of anti-tumour effect and reducing late morbidity. In order to maintain an iso-effect in the tissues, the total dose has to be increased due to the sparing effect of the smaller fractions (146). In the past hyperfractionated radiation has not been shown to hold any benefit over conventionally fractionated radiation when used alone (148) or in conjunction with chemotherapy (18;149). More recently (2003) HIT-SIOP PNET 4 (146), a prospective randomised controlled trial of hyperfractionated versus

conventionally fractionated radiotherapy in standard risk medulloblastoma was started in order to compare the event free survival rate for children and adolescents with standard risk medulloblastoma (Table 6). This trial has now closed, having recruited the required number of patients and the data is being analysed.

Intensity-modulated radiation therapy (IMRT) is a modern conformal technique that employs fused digital imaging, multiple beam angles, varied exposure times and energy beams shaped by dynamic multi-leaf collimators to deliver radiation to a tightly defined area, with the goal of reducing normal tissue radiation exposure. One of the main benefits of IMRT use in medulloblastoma is the avoidance of cochlear irradiation, hence reducing the incidence of hearing loss (150).

Radiotherapy for medulloblastoma causes severe damage to the developing brain. Radionecrosis, mineralizing microangiopathy and calcification of the brain, hypopituitarism (growth hormone, FSH, LH deficiency) hypothyroidism, cataracts and ototoxicity are well documented long term complications of radiotherapy for paediatric brain tumours (151). Perceptual motor task performance was below average in more than 50% of the participants in the series by Johnson et al, but motor dexterity was more severely affected than perception. Also, the majority of the participants developed learning difficulties and had delays in both physical growth and

development (152). Grill et al reported that there is a significant correlation between the full-scale IQ score and the craniospinal radiation dose, with mean FSIQ scores at 84.5 (SD= 14.0), 76.9 (SD= 16.6), and 63.7 (SD= 15.4) for 0 Gy, 25 Gy, and 35 Gy of craniospinal radiation respectively. A marked drop in verbal comprehension scores was noted in children who had received the higher dose. Subsequently, Grill et al supported the rationale for decelerating the dose escalation of craniospinal radiation doses and volumes in standard-risk posterior fossa tumours (153).

In the CCG 9892 study, the neuropsychological effect of 23.4 Gy craniospinal radiation was reported to be a decline of 4.3 FSIQ points per year. Females were more subject to verbal IQ decline than males, and young children (< 7 years of age) were more adversely affected than older children, with a significant decline in non verbal IQ (124).

Table 6. The doses of radiotherapy for each arm in HIT-SIOP PNET 4

(146)

HFRT (experimental arm)	Conventionally fractionated radiotherapy (standard arm)
Craniospinal axis: 36 Gy in 36 twice daily fractions of 1 Gy	*Craniospinal axis:* 23.4 Gy in13 daily fractions of 1.8 Gy
Post fossa: 60 Gy in 60 twice daily fractions of 1 Gy	*Post fossa:* 54 Gy in 31 fractions of 1.8 Gy
Tumour bed: 68 Gy in 68 twice daily fractions of 1 Gy	

1.9.3. Chemotherapy

The use of chemotherapy was a major advance in the treatment of medulloblastoma (72). In the 1980s, the debilitating cognitive and endocrinological sequelae of craniospinal radiotherapy in addition to the poor survival rates for children with postoperative residual tumours led to successive randomized co-operative trials by the International Society of Paediatric Oncology (50), the Children's Cancer Group (CCG 942) (48) , and the Paediatric Oncology Group (POG 7909) (154) which introduced chemotherapy to improve survival, and later, reduce radiation dosage. At first, an increase in overall survival from chemotherapy was not apparent for all children, but only those who had bulky residual tumour or metastatic disease. Subsequently in the 1990s, the single-arm study CCG 9892 was performed and used 23.4Gy craniospinal irradiation rather than the standard 36 Gy, followed by eight courses of lomustine (CCNU), cisplatin and vincristine for children aged 3 to 10 years without residual tumour or metastases. This study attained a remarkable 5 year event-free survival (EFS) of 78% of children (155).

In both CCG 921 and the German trial HIT'91, overall survival was not significantly different in children who were staged as having no metastasis or microscopic metastasis (55;96). Children younger than 3 years are always considered to be at high-risk because of their well established higher rates of

recurrence in this group of patients (78). Brain stem invasion (described as Chang stage T3b) was previously considered to be a high-risk indicator is thought now not to affect prognosis (55).

The SIOP / UKCCSG PNET-3 Study is the first large multicenter randomized study which demonstrated improved EFS for pre-radiotherapy chemotherapy compared with RT alone in patients with non metastatic medulloblastoma (Change stage M0-1). Chemotherapy regime comprised of vincristine 1.5 mg/m² weekly for 10 weeks; four cycles of etoposide 100 mg/m² daily for 3 days on weeks 1, 4, 7 and 10; carboplatin 500 mg/m² daily for 2 days on weeks 1 and 7, and cyclophosphamide 1.5 g/m² on weeks 4 and 10. This study included patients aged 3 to 16 years inclusive. They were randomly assigned to receive 35Gy craniospinal radiotherapy in 21 fractions, followed by a posterior fossa boost of 20 Gy in 12 fractions or chemotherapy, followed by the radiotherapy.

It recruited 217 patients randomly assigned to treatment. 179 (82.5%) patients were eligible for analysis [chemotherapy and radiotherapy, 90 (50.3%) patients; radiotherapy alone, 89 (49.7%) patients]. The median age was 7.67 years and the median follow-up was 5.40 years. Overall survival at 3 and 5 years was 79.5% and 70.7% respectively. EFS at 3 and 5 years was 71.6% and 67.0% respectively. EFS was significantly better for the chemotherapy and radiotherapy group (p= 0.0366) as demonstrated by an EFS of 78.5% at 3

years and 74.2% at 5 years compared with 64.8% at 3 years and 59.8% at 5 years for radiotherapy alone group. However, there was no statistically significant difference in 3 year and 5 year overall survival between the two groups (p= 0.0928). Multivariate analysis identified use of chemotherapy (p= 0.0248) and time to complete radiotherapy (p= 0.01) as having a significant effect on EFS (121).

Overall survival and EFS were significantly better for patients completing radiotherapy within 50 days compared with those requiring >50 days to complete radiotherapy (3-year overall survival rate of 84.1% vs. 70.9%, p= 0.0356, 3-year EFS rate of 78.5% vs. 53.7%, p= 0.0092). Multivariate analysis identified the use of chemotherapy (p= 0.0248) and radiotherapy duration (p= 0.01) as predictors of better EFS. Posterior fossa recurrence occurred in 11 (34.4%) of 32 with a posterior targeting deviation compared with 13 (16.3%) out of 80 without (p= 0.043). The results of this study have confirmed the importance of the duration of radiotherapy treatment for children with medulloblastoma. Attention to detail is also important when planning radiotherapy, as illustrated in the case of posterior field placement (156).

In the same study (SIOP / UKCCSG PNET-3 Study) but looking at Chang stage M2-3 stage patients with medulloblastoma who were treated with surgery and pre-radiotherapy chemotherapy, at a median follow-up of 7.2 years the overall survival rates at 3 and 5 years were 50.0% and 43.9,

respectively, while EFS rates at 3 and 5 years were 39.7% and 34.7%, respectively. Univariate analysis did not demonstrate any impact of age, gender, M stage, extent of resection, radiotherapy duration or metastatic boost. For patients who commenced radiotherapy within 110 days of surgery, EFS was significantly (p= 0.04) worse than for those who commenced radiotherapy later than this. Chemotherapy was not shown to improve the outcome for stage M2 - M3 patients when compared with earlier multi-institutional series (157).

The SFOP study on young children with medulloblastoma recruited 79 children aged younger than 5 years who had had surgical resection of medulloblastoma. Patients were treated with combination chemotherapy which did not include methotrexate, for more than 16 months irrespective of the extent of disease. Salvage therapy (including radiotherapy) was indicated only for disease progression or relapse during or after the end of chemotherapy. A second operation was considered in patients with local relapse or progression. In this study, the 5-year overall survival was 73% in the R0M0 (no residual disease, no metastasis) group, 41% in the R1M0 (radiological residual disease alone) group, and 13% in the RXM+ (presence of metastasis) group. It was reported that conventional chemotherapy alone can be used to cure children with non-metastatic medulloblastoma who have gross total resection confirmed by early radiological assessment, but is not sufficient for treatment of those with metastatic or incompletely resected

medulloblastoma. Salvage treatment followed by posterior fossa radiotherapy can effectively treat local relapses or progression (88).

1.9.3.1 High-Risk Disease

When dealing with patients with high risk disease, current clinical trials employing radiation therapy include the use of radiosensitizing chemotherapy or post-radiotherapy high dose chemotherapy utilizing peripheral blood stem cells rescue (PBSC) in patients greater than 3 years of age. The COG 99701 study uses carboplatin and vincristine concurrent with irradiation followed by a randomization between cyclophosphamide and vincristine or cyclophosphamide, vincristine and cisplatin. Post-irradiation chemotherapy has been demonstrated to be feasible with a regime using pre-irradiation topotecan followed by PBSC harvest, radiation therapy and four consolidation courses of vincristine, cisplatin and cyclophosphamide supported by PBSC rescue (158). The COG 99702 protocol uses vincristine concurrent with radiation followed by three cycles of high-dose chemotherapy (two cycles of carboplatin and thiotepa and one of carboplatin, cyclophosphamide and vincristine) supported by PBSC rescue (18).

In children less than 3 years of age, chemotherapy has been used in an attempt to delay or eliminate the need for radiation because the use of radiotherapy is contraindicated owing to its severe long-term neurocognitive sequelae.

In 1986, the POG began a study for children under 36 months of age with malignant brain tumours. These children were treated postoperatively with combinations of two 28-day cycles of cyclophosphamide / vincristine followed by one 28-day cycle of cisplatin / etoposide. This sequence was repeated until the disease regressed or for 1 or 2 years depending on the age at diagnosis (roughly until the age of 3 years). Following this, patients received radiation therapy. The response rates were highest among patients with medulloblastomas, malignant gliomas and ependymomas. The progression-free survival rate was 41% at one year for children who were 24 to 36 months old at diagnosis and 39% at two years for those under 24 months of age at diagnosis. Multivariate analysis identified embryonal tumours as a significant adverse prognostic feature and complete resection as a favourable feature. Complete responses to chemotherapy were associated with a progression-free survival rate approaching that achieved with gross total resection (94).

The CCG trial used an eight-drug chemotherapeutic regime including vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytarabine, prednisone and cyclophosphamide for patients less than 3 years of age following surgery and postoperative staging, 56% of whom had

medulloblastoma. Objective tumour response was noted in 28% of all patients following two cycles of chemotherapy. The 3-year PFS rate for medulloblastoma was 22% ± 6% (159).

Rutkowski et al found that postoperative chemotherapy alone is a promising treatment for medulloblastoma in young children without metastases (89). They conducted a trial using intensive postoperative chemotherapy alone. Forty-three children received three cycles of intravenous chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, and etoposide) and intraventricular methotrexate postoperatively. The five-year progression-free and overall survival rates (+/-SE) in children who had complete resection (17 patients), residual tumour (14), and macroscopic metastases (12), were 82% +/-9% and 93%+/-6%, 50% +/-13% and 56% +/-14%, and 33% +/-14% and 38% +/-15%, respectively. The five-year progression-free and overall survival rates (+/-SE) in 31 patients without macroscopic metastases were 68% +/-8% and 77% +/-8%, respectively. They found that desmoplastic histology, metastatic disease and age younger than two years were independent prognostic factors for tumour relapse and overall survival. Asymptomatic leukoencephalopathy was detected by MRI in 19 (82.6%) out of 23 children. After treatment, the mean IQ of these children was significantly lower than that of healthy controls within the same age group but higher than that of patients in a previous trial who had received radiotherapy (89).

A SFOP trial treated relapsed medulloblastoma patients who were less than 3 years of age and who had not received previous radiation with a conditioning regime of busulfan and thiotepa followed by autologous bone marrow transplantation. After recovery, patients with focal disease received local radiotherapy to the posterior fossa. A response rate of 75% was noted in patients with assessable disease. EFS rate was 50% at a median follow-up of 31 months (160).

1.9.3.2. Relapsed Disease

Relapsed medulloblastoma remains very difficult to treat despite its relative chemosensitivity. Although responses have been noted with multiple single agents including cyclophosphamide, cisplatin, methotrexate, carboplatin and oral etoposide, tumour recurrence is inevitable (18).

Modest success however has been achieved with high-dose regimens that are supported by PBSC rescue. A CCG pilot study using a single cycle of high-dose carboplatin and thiotepa followed by PBSC infusion, demonstrated objective responses in one third of patients with PNET / MB but also a high incidence of complications due to drug toxicity and a mortality rate of 16%. It was also noted that patients with minimal residual disease experienced the greatest survival benefit (P < 0.0005) (161). In a follow-up CCG study, 23 patients with relapsed medulloblastoma received a high-dose chemotherapy

regimen consisting of carboplatin, thiotepa and etoposide with PBSC rescue resulting in a 3-year event free survival of 34% and a 3-year overall survival of 46% (162).

1.9.4. Genetic treatment

Molecular genetics is providing insight into the mechanisms whereby tumour cells achieve and maintain escape from normal growth controls, gain metastatic potential and affect drug resistance. Therapeutic targets are being exploited with antibody-conjugated agents as well as small molecule inhibitors in the setting of phase I/II clinical trials. Among the agents being evaluated for medulloblastoma therapy is Erlotinib, an inhibitor of the ErbB2 receptor (163). SCH66336 is an oral farnesyl transferase inhibitor that blocks the activity of the proliferative Ras pathway (164). Lastly, gefitinib inhibits the activity of the PDGF receptor, which induces proliferation through the Ras/MAP kinase pathway. While efficacy data is not available, phase I trials are demonstrating minimal drug toxicity in the patients (18). Rood et al reported that future use of these agents is likely to include combinations of drugs to block the pathways at multiple signalling levels or to inhibit different pathways. These agents used in combination with conventional cytotoxic chemotherapy is another attractive option to enhance therapeutic efficacy with minimal escalation of toxicity (18).

1.10. Justification

In order to evaluate the response of medulloblastoma to treatment and to improve the patient's outcome, a series of various staging systems have been reported in the literature and used in clinical practice over the past few decades (20;41;44;55;58;63;87;99;165-167). Various types of data (demographic, operative, histopathological and genetic) have been used in various combinations in these staging systems, suggesting that currently there is no perfect staging system for medulloblastoma. Consequently there is a need for the development of a more accurate staging system, which will help to optimise the decision making process and improve outcomes.

In Chang's staging system (20) the limit of 3 cm in tumour diameter was used in order to distinguish the different T stages (T$_1$ from T$_2$ stage), but the rationale for the selection of that figure as a cut off remains unclear. However, it was demonstrated that patients with early lesions (T$_1$ and T$_2$) responded to radiotherapy much more favourably compared to late lesions, T$_{3b}$ and T$_4$. This highlights the significance of the size of the primary medulloblastoma in patient outcome (20). The above conclusion was re-confirmed in a further study by Harisiadis et al nine years later (63).

Similarly, the MAPS staging system (41) when measuring residual tumour, uses a figure of 1.5 cm to differentiate between stage S1 and S2. The rational of this is again unclear.

Chang et al had stated that attempts at radical surgical resection of medulloblastoma should be avoided as it is a radiosensitive and radiocurable tumour (20). More recently, Kombogiorgas et al also reported a series of children with medulloblastoma from Birmingham Children's Hospital with similar 5-year survival rates in patients with total and sub-total excision of medulloblastoma at 61.1% and 61.8% respectively (103).

The absence of significant differences in survival between patients with total or sub-total excision of medulloblastoma strengthens the view that total excision of medulloblastoma can be avoided when the risk for potential intra-operative damage and subsequent neurological deficits is high. In current neurosurgical practice, the goal of surgical resection is complete removal of tumour whenever possible, accepting a certain degree of postoperative morbidity (18;89). Operative attempts to excise medulloblastoma from the brain stem is associated with an increased risk of neurological deficits of a temporary or sometimes permanent nature, even when the surgeon is aided by modern adjuncts such as evoked potential monitoring (125). Postoperative complications and neurological deficits resulting from surgery not only impact

upon quality of life but may also contribute to the delay in commencing necessary adjuvant therapy.

Another problem with the current staging systems of patients with medulloblastoma is lack of universal consensus regarding the classification of the degree of tumour excision (30;48;48;52;89;121;125;168). Sutton et al defined total resection in the strictest sense as the absence of visible tumour in the operative bed as well as the absence of tumour on postoperative enhanced MRI scans. A resection is deemed subtotal if the surgeon felt that a small amount of tumour had been left insitu or if the postoperative scan shows areas of enhancing tissue in the tumour bed (125). Albright et al defined the degree of tumour excision (Table 4) as total when no visible tumour is evident at the completion of resection; near-total when more than 90% resection of the primary tumour was achieved but visible tumour remains and subtotal when 51-90% resection has been achieved (52). In other series the degree of tumour excision is defined in broader terms such as subtotal excision if more than 50% of the primary tumour has not been resected (48) or as complete and incomplete resection (89). Over the last 20 years, various series have reported less than total/subtotal excision in 24%-80% of patients operated for medulloblastoma (47;48;52;88;96;121;169), which makes the comparison of patients' outcomes between the different series inaccurate.

It has become clear that post-operative imaging studies is superior to the subjective impression of the surgeon in estimating the extent of resection of posterior fossa tumours (125). The current method of radiological estimation of postoperative residual medulloblastoma also does not provide information about the total volume of residual tumour (52;89;157), as it measures only the cross section of the largest demonstrated part of residual tumour in a single axial MR slice (52;89). Subsequently, further smaller residuums which are demonstrated in different slices of MR scan series are not included in the estimation of the size of the total residual tumour.

Since the 1980s, with the introduction of the MAPS staging system, the postoperative residual tumour volume has been reported in many studies as an independent prognostic factor in the outcome of patients with medulloblastoma (44;46;50;52-55). In all of these studies the assessment of tumour size was done by measuring the maximum diameter of tumour on axial views on CT or MR scans resulting in an underestimation of the actual size of the residual medulloblastoma.

The need for a new study to determine a more accurate method of assessment of residual tumour is required. In this study a MR image analysis method was used to measure the volume of primary and residual medulloblastoma on pre-

and immediate postoperative MR scans respectively, in order to examine the relationship between the degree of surgical excision and outcome.

A knowledge of the maximum volume of residual tumour that may be left unresected at the tumour bed without significant detriment to outcome provides neurosurgeons with a clearer and more practical view of the operative goal. It may also direct the potential need for "second look" operations in the event of large residual tumour volume being found on the immediate postoperative MRI scan.

1.11. Aim of the study

This study aims to re-evaluate the role of residual disease following primary operative treatment for medulloblastoma as a risk factor for patients' outcome by evaluating the absolute volume of primary and residual tumour and residuum tumour ration. This avoids the described flaws of previous studies as it does not assess only a fraction of residual medulloblastoma on immediate postoperative MR scan but its total volume. It is a *pilot study* which will estimate the required prerequisites for a further larger study of the role of volumetrically assessed residual tumour in clinical outcome of children with

medulloblastoma. The need for this pilot study arises from the absence of any relevant published study or data.

In this study, volumetric measurement of the tumour residuum was correlated to survival rates. Potentially, the results could also affect the decision to re-operate on some patients with residual tumour.

Currently, a significant residuum is arbitrarily defined as that with a maximum cross-sectional area of greater than 1.5 cm² (55) on the immediate postoperative MR scan. These patients are classified as high risk requiring more aggressive adjuvant treatment (18;43;99).

The CCG 921 Randomized Phase III Study (55) was the trial which introduced the value of 1.5 cm² of residual tumour on cross section of immediate postoperative CT or MR scan as a limit for the risk stratification of patients. Based on that study, patients with residual tumour of ≤1.5 cm² on immediate postoperative MR or CT scan fall into the low risk category for tumour recurrence and those with residual tumour of > 1.5 cm² are considered to be high risk patients for tumour recurrence (55).

In clinical practice, neurosurgeons routinely use a percentage in order to express the extent of brain tumour resection. In this study, the value of 15% was used as a cut off point in order to compare survival rates. Patients with a postoperative residual tumour volume of less or equal to 15% and more than

15% of primary medulloblastoma volume were considered low and high risk respectively. The consensus view of experienced paediatric neurosurgeons was that the final 15% of medulloblastoma was the most difficult to remove hence the figure selected. This study aimed to test if a greater than 15% residual tumour volume was an adverse prognostic feature. The study was designed to test the null hypothesis; that there was no difference in outcome between these two groups. Patients were divided into two arms:

1. The first arm included children with residual tumour of ≤15% of primary medulloblastoma volume.
2. The second arm included children with residual tumour >15% of primary medulloblastoma volume.

Estimation of achieved tumour resection as a percentage of the primary tumour volume is difficult and depends on knowing the original tumour volume. The volume of large residual ratio (percentage) of small primary tumours might be less than the volume of small ratio (percentage) of large primary tumours. In order to solve the above problem, the absolute values of residual tumour volume were measured in cm³ and were used to find a correlation between residuum tumour volume and outcome.

Chapter 2

2.1. Patient population

The patients participating in this study were recruited from Birmingham Children's Hospital, Birmingham, U.K. and Hôspitale Necker-Enfants Malades and Institute of Gustave-Roussy, Paris, France.

Each child treated at Birmingham Children's Hospital with a brain tumour is registered routinely with the Cancer Registry of Birmingham Children's Hospital and the UKCCSG Registry upon admission and diagnosis. Patients were recruited from the computer database of the Cancer Registry at Birmingham Children's Hospital and actively followed up in the Oncology and Neurosurgery Clinics.

Each child treated at Hôspital Necker-Enfants Malades with a brain tumour is registered routinely with the SFOP Registry upon admission and diagnosis. Patients for this study were recruited from the computer database of the Institute of Gustave-Roussy Registry and actively followed up in Oncology and Neurosurgery Clinics.

All children treated at Birmingham Children's Hospital between 1999 and 2006, and Hôspital Necker-Enfants Malades and Institute of Gustave-Roussy

in Paris between 2002 and 2005 for medulloblastoma have been followed up until the time of writing or death. All significant clinical events have been recorded.

The study series has 37 children in total. 25 of children were treated at Birmingham Children's Hospital between 1999 and 2006 and 12 children were treated in Hôspital Necker-Enfants Malades and Institute Gustave-Roussy between 2002 and 2005.

The end point in the study is the date of most recent follow up for patients who were alive at the time the thesis is written or the date of death for patients who died. 25 children were eligible to be studied from a series of 42 children who received operative and oncologic treatment at Birmingham Children's Hospital between 1999 and 2006. 12 children were eligible to be studied from a series of 53 children who received operative treatment at Hôspital Necker-Enfants Malades and oncological treatment at the Institute Gustave-Roussy between 2002 and 2005.

The reasons of exclusion of patients from the study were as follow:

1. Absence of available preoperative or immediate postoperative MRI scans data in DICOM form (Chart 1).

It was impossible to retrieve either the preoperative or postoperative MR scans in DICOM form in 15 patients from BCH and 37 patients from Necker-IGR Hospitals (52 cases in total) because of:

a) Loss of some optic discs that the MR scans were stored in DICOM form

b) Incompatibility of the old optic discs of Necker Hospital with its new MR scanner. Also, in some cases the first postoperative MR scan was performed after the commencement of adjuvant treatment. Subsequently those cases were excluded from the study as they did not fulfil the selection criteria of the study.

2. Absence of clinical information regarding the treatment protocol of the patients (unobtainable medical notes in 6 cases).

2.2. Ethical approval

Application for ethical approval for the current research project was submitted to the South Birmingham Local Research Ethics Committee. The application form set included copies of:

1. Parent / Child consent form.

2. Family Doctor Information Sheet.

3. Patient / Family Information Sheet.

4. Thesis-Research Project Outline.

5. Study Participant Invitation Letter.

Ethical approval was obtained from the South Birmingham Local Research Ethics Committee permitting completion of the current research project.
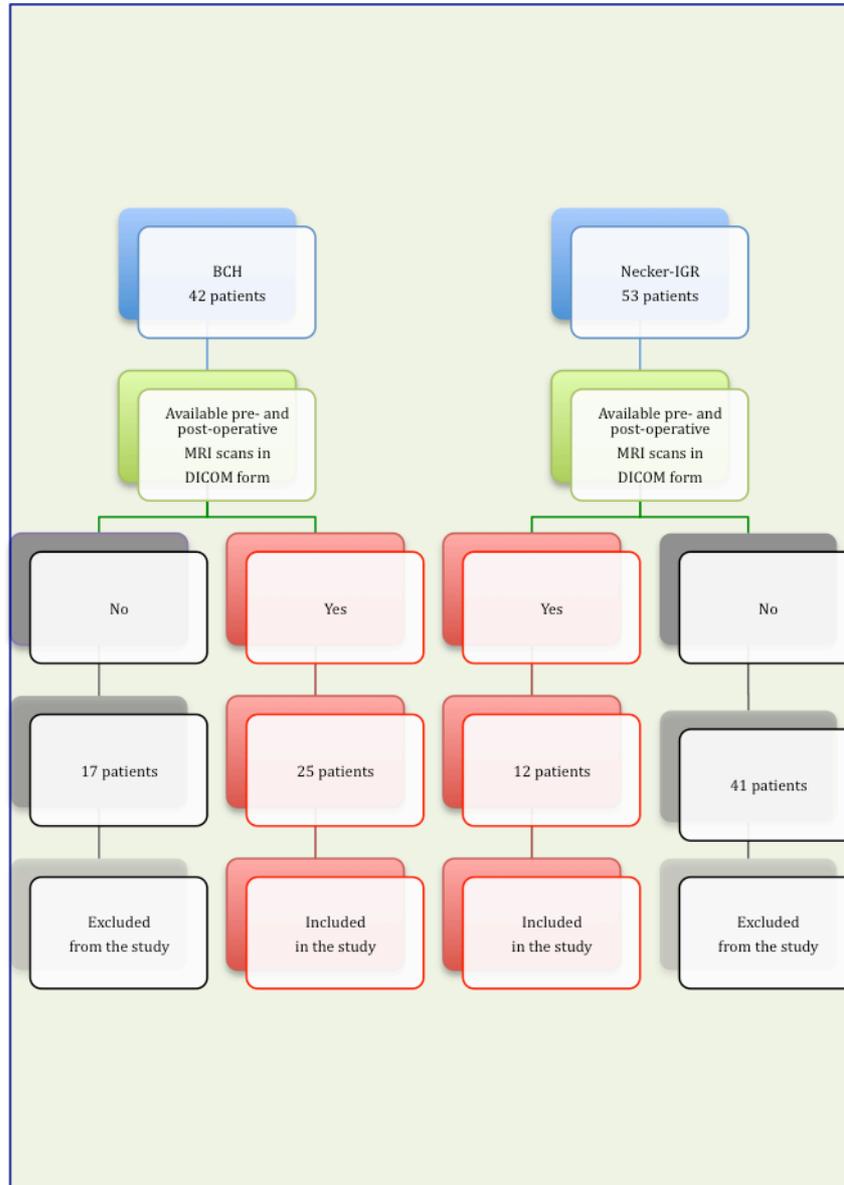
Chart 1. Algorithm of selection process of eligible patients for study based on availability of pre- and post-operative MRI brain in DICOM form

2.3. Patient selection criteria

2.3.1. Inclusion Criteria

The inclusion criteria were:

1. Patients with a histologically confirmed diagnosis of medulloblastoma (29).

2. Patients aged less than 16 year of age at the time of histological diagnosis.

3. A complete set of MR brain examinations before and after primary posterior fossa surgery available in DICOM form (minimum modalities of examination: Axial T1W with contrast enhancement and Axial T2W sequences).

2.3.2. Exclusion criteria

The exclusion criteria were:

1. Patients with no immediate postoperative MR brain.

2. Unavailability of a complete set of MRI of the brain in DICOM form (Chart 1).

3. Patients older than 16 years of age at the time of histological diagnosis.

4. Patients previously treated for medulloblastoma.

2.4. Methodology

The study required an accurate estimation of medulloblastoma volume, which was achieved by using image analysis from the neuroradiological examinations for every patient. Calculation of medulloblastoma volumes was achieved after image analysis of preoperative and immediate postoperative MR scans of each patient by using segmentation techniques. Preoperative and immediate postoperative medulloblastoma volumes were then plotted against age for analysis. This created a scatter plot demonstrating the pre and post primary surgical excision volumes of each patient with medulloblastoma. Statistical calculations were then performed to correlate the extent of tumour excision to outcome. The categorical data (alive-dead) of two patient groups/arms (i.e. residual tumour ratio more or equal-less than a specific limit) was calculated using chi-squared test and Fisher's exact test. 5-year survival data was analysed using the Kaplan-Meier method. This method was chosen over logistic regression or comparison of the mean time to reaching the endpoint in patients with and without a new treatment to avoid problems of

censored data within the latter. The log-rank test was used to address the null hypothesis which states that there are no differences in survival times in the groups being studied, and compares events occurring at all time points on the survival curve. However, as the log-rank test is unable to assess the roles of independent factors against the endpoint, a regression model (i.e. cox regression analysis) was used to quantify the relationships between one or more potential significant prognostic factors of patients' outcome (i.e. gender, age, presence of metastasis at the time of diagnosis). Finally, a Receiver Operating Characteristic (ROC) curve was used to assist in the selection of the optimal residual ratio and residual volume cut-off value.

The minimum required number of patients for the study was calculated by power analysis. The research study outline was submitted to The Division of Neuroscience of Medical School of the University of Birmingham and was externally peer-reviewed and deemed suitable for the purpose of an MPhil study.

2.5. Image analysis technique and tumour volume measurement

Segmentation technique is the process whereby a composite CT or MR image is broken down to several simple images which can be easily manipulated and reconstructed in three dimensions. In this study, every MR image is comprised

of a matrix of pixels which is usually square; for example 256 x 256. Each of these pixels has a unique grey value within a predetermined range. Because this range is much wider for MR images, different brain structures are imaged as subtle differences of grey signal. Segmentation allows grouping of pixels into regions, hence defining the boundaries of different structures (170).

The segmentation technique has been used in many other neurosurgical studies in the past (114;171-178), including measurements of tumour volume and its response to therapy (170;179). Recently, Mariani et al studied the impact of tumour volume and surgical resection on the long-term outcome of patients with supratentorial, diffuse, WHO grade II astrocytomas and oligo-astrocytomas by using image analysis (180). Also, Xie et al reported the development of a semi-automated MR image analysis method for brain tumours, which can be used as a staging procedure and a method of evaluating tumour response to treatment in clinical practice (181).

There are three methods of segmentation techniques; manual (supervised) (182;183), semi-automatic and automatic (the latter two methods are unsupervised) (170). The semi-automatic method requires operator intervention in order to complete the process. The automatic method is operator independent (170). In this study, the semi-automatic method was used to outline the tumour edges and distinguish it from the adjacent

65

structures such as surrounding oedema of the cerebral tissue, scar tissue or blood clots.

Variability in serial volume measurements and inconsistencies between observers have been reported in the literature in studies involving tumour volume measurement methods employed to assess tumour response to treatment or to plan treatment (170;184;185). The manual method of tumour volume measurement is potentially subjective and prone to large variations in intra- and inter-operator performance. Joe et al compared the manual and semi-automatic methods of brain tumour volume measurement (186). They reported that the semi-automated computer method of measuring tumour volume has similar reliability compared with the manual trace method but is faster. It is regarded as an alternative method to manual tracing for measuring serial tumour volumes in patients with high grade brain neoplasms (186).

Shan et al reported the development of a robust and accurate automated method for identification of the cerebellum on MR images of patients with medulloblastoma. This method may be applied to investigations that require segmentation and quantitative measurement of MR images of the cerebellum (187). However, the manual segmentation technique was employed as:

1. It can differentiate and trace boundaries of tumour from oedema or residual tumour from haemorrhage with greater accuracy (181;188). The assistance of T2W MR images was used in difficult cases.

2. The segmentation technique used in this study has been previously used in the Informatics Laboratory at The Institute of Child's Health in Birmingham in other research projects (173-178;189) and has proven to be accurate and reliable. This is particularly shown in a previous study measuring changes in intracranial volume in childhood (172). In this study, patients had ordinary MR sequences (5 mm slice thickness and 2 mm interval slice thickness (5/2) and volumetric coronal MR sequences consisting of 124 contiguous slices of 1.5 mm thickness (1.5/0). In these patients, intracranial volume calculated by measuring 19 axial T2W slices (5/2) and was compared with volumes calculated by measuring T1W slices (1.5/0). In all cases the difference was less than 5% ranging from 0.06% to 4.5% (mean 2.8%) (172).

The use of MR segmentation technique has been validated by the methods outlined below:

1) Phantom models (object filled with known volume of water) when repeated measurements are performed by the same or different operators.

2) Additional software in order to prevent mis-calibration of operating image analysis program.

However, the measurement of tumour volume by image analysis is limited by the inability to measure tumour tissue that escapes from MR discriminative sensitivity. In practice, MR scan does not pick up tumours with a thickness of less than 2 mm.

The segmentation software used for this study was designed by members of the Department of Computer Science at the University of Birmingham (190-194) and has been in continuous use since 1995 in numerous research projects (171;173-178;189;193). It has the ability to manipulate a variety of digital images, including CT and MRI. It operates on a Sun workstation (Sun Microsystems, California, USA) situated at the Neuroscience Informatics Laboratory of The Institute of Child Health at Birmingham Children's Hospital and is connected via Local Area Network to the consoles of the MRI and CT scanners. Thus, images can be imported to the workstation via the network but also from external sources such as CDs or DVDs. Any form of digital imaging from any source can be used.

The computer assisted image analysis was performed using the MR brain scan data stored in DICOM format. After importing the images to the software, segmentation was performed. The interface between tumour (primary or residual medulloblastoma) margin and the surrounding cerebellum was outlined in each slice of gadolinium enhanced T1W MR image of brain scan. For those cases in which there were difficulties in distinguishing the tumour

boundaries from their associated surrounding oedema T2W images were also reviewed. This enabled comparison with gadolinium enhanced T1W MR images, in order to avoid inclusion of the surrounding oedema within the outlined tumour perimeter. After outlining the cross section of the tumour (Figure 4), the system calculated the outlined area in mm² and multiplied this by the slice thickness to calculate the volume of each slice. The total volume of the primary or residual tumour was calculated by adding the volume of all slices.

MRI scans for this study included some preoperative images with a thickness of 5 mm and an interval of 1.5 mm (5/1.5) between slices (MR series of 19 slices) and in other patients with volumetric series of 108 slices (images with a thickness of 1.62 mm each and absence of interval gap between them: 1.65/0). Postoperative MR scans amounted to 19 slices in all cases. The validation of measurement accuracy between MR scans of 19 and 108 slices has been completed and found to be satisfactory (172). The volume of the interval slice was calculated using the surface areas of the preceding slice and subsequent slice along with the thickness of the interval slice (1.5 mm) as follows:

volume of interval slice = [(surface area of preceding slice + surface area of subsequent slice)/2] x 1.5

in which *(surface area of preceding slice + surface area of subsequent slice)/2* is the mean of the two adjacent slices, which corresponds to the surface area of the interval slice multiplied by 1.5 (the thickness in millimetres) used to calculate the volume of the tumour.

The medulloblastoma volume is calculated in two stages:

i.   The preoperative volume (Vol. Pre),

ii. The immediate postoperative volume (Vol. Post)

The immediate post-operative MR brain scans were done within 48 to 72 hours of primary tumour excision.

The residuum ratio is calculated as follows:

Residuum ratio (RR)= Postoperative Volume / Preoperative Volume.

This describes the amount of residual tumour after primary excision.

(a)

(b)

Figure 4. Outlined boundaries of medulloblastoma (a) primary tumour, preoperatively, (b) residual tumour, postoperatively.

2.6. Power Analysis

A power analysis was performed in order to estimate the number of patients required for this study. In the last 40 years, the survival rate of medulloblastoma has improved as a result of radical surgical excision of the tumour along with adjuvant treatment (radiotherapy to the craniospinal axis, with or without chemotherapy). However, there is considerable variation on the survival rates reported from various centres with reports of overall 5-year survival ranging from 32% to up to 83% in different studies (47;49;50;52;63;89;195-199). In the more recent studies the overall 5-year survival of children with medulloblastoma is reported as approximately 70% (47;52;89;195;199).

The number of patients required to be recruited for the current study was calculated by using a software for statistical power analysis and sample size determination (Query Advisor®, Statistical Solutions Ltd, Cork, Ireland). The calculation is as follows: for maximum probability of rejecting the null hypothesis when it is true [Type I / alpha (α) error] with an alpha value of 0.05, and also the probability of not rejecting the null hypothesis when it is false [Type II / beta (β) error] with a beta value of 0.2 and a power of the test of 80%, the minimum sample required for each group is 18 patients to detect a minimum difference of 50% in survival, with a standard deviation of 5% for residuum ratio. The available number of patients for each group in this study

therefore satisfies the minimum requirements needed.

2.7. Statistical analysis

Statistical analysis was performed using SPSS software programme [version 16.0, SPSS Inc, USA, 2007]. Chi-square was used to identify factors of significance. Logistic regression analysis was used to investigate the effect on survival of all variables that proved significant on chi-square. Analysis of Variance (ANOVA) was used to compare mean values and Kaplan-Meier survival analysis was performed for each subgroups. Kaplan-Meier survival analysis was used for each individual factors and Cox-regression analysis for multifactorial survival analysis. Significance was set at p= 0.05.

Population characteristics were studied including the following variables: age at diagnosis, gender, duration of symptoms, presence of metastasis or hydrocephalus at time of diagnosis, extent of resection, postoperative adjuvant therapy i.e. radiotherapy and / or chemotherapy. The follow up period was defined as the period from the date of diagnosis up to the date of last medical review of patient or the date of death of patient.

In order to compare the degree of surgical excision of medulloblastoma with patients' actuarial survival the following values of Residuum Ratio (RR: Vol

Post / Vol Pre) were used as a cut off: *15%* based on the study null hypothesis. Also, another two cut off values were also studied, which have been used in clinical practice in patients' staging process and used in published trials as:

1) *10%* rate from Children's Cancer Group-921 study of the extent of medulloblastoma resection (52)

2) *1.5 cm³* based on the Children's Cancer Group -921 Randomised Phase III Study (55), as that study used the 1.5 cm² of surface area of residual tumour as cut off. If it is considered theoretically that the residuum has spherical shape then for its largest circle surface size of 1.5 cm² the corresponding sphere volume will be 1.38 cm³ ≈ 1.5 cm³.

In addition, the overall 5-year survival and mortality rates were correlated to gender, age at the time of diagnosis for patients above and under 3 years and the preoperative tumour volume (absolute value).

Chapter 3

3.1. Population

From the study series of 37 children with medulloblastoma, there were 26 (70%) males and 11 (30%) females (ratio of 2.3:1), Figure 5. This is in keeping with reports in the literature which cite a male preponderance demonstrated by a male to female ratio of 2:1 (11;15). The patients age at the time of diagnosis ranged between 7 months and 181 months (median: 67 months, mean: 76.9 months and SD: 46.6 months). Thirty (81%) patients were over the age of 3 years and 7 (19%) under the age of 3 years at the time of diagnosis, Figure 6. The follow up period for all patients ranged from 6 months to 117 months (mean: 45 months, SD: 31 months). The mean follow up time for the patients alive was 65.4 months (range: 36 - 117 months, SD: 23.8, median: 56 months). 15 (40.5%) of 37 patients died during in follow up period. The mean survival time of deceased patients was 15.5 months (range: 6 - 29 months, SD: 6.5 months, median: 14 months). The minimum follow up time for the patients alive was 36 months which exceeded the maximum survival time of deceased patients. Table 7 is a list of the all patients in this study demonstrating (presented with a code number: P1, P2, etc., P: studied patient) and incorporating the details of gender, follow up time (in months), and if the patients were alive or deceased at the time of latest notes review. Patients are listed in age order.
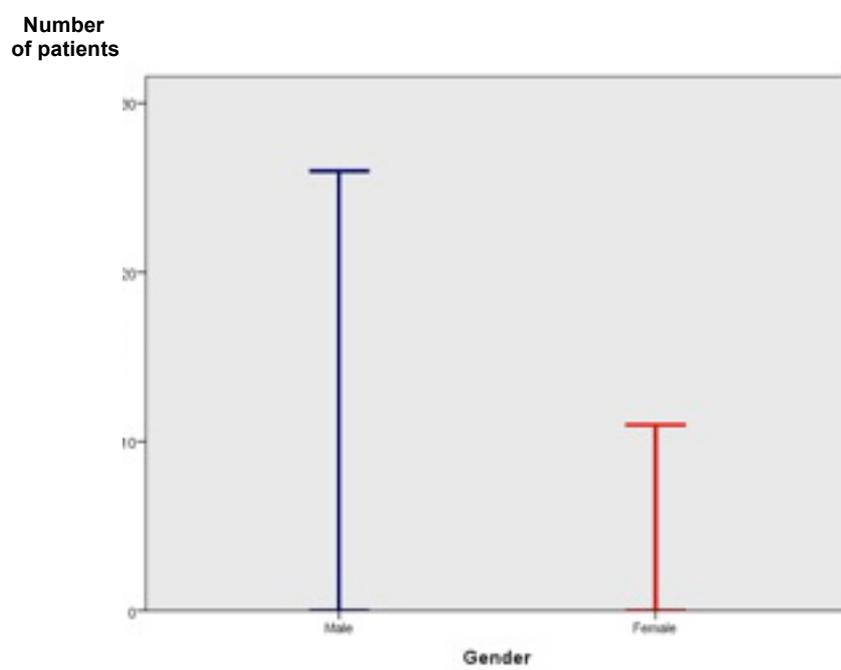
**Number
of patients**

**Figure 5. Gender of patients.**
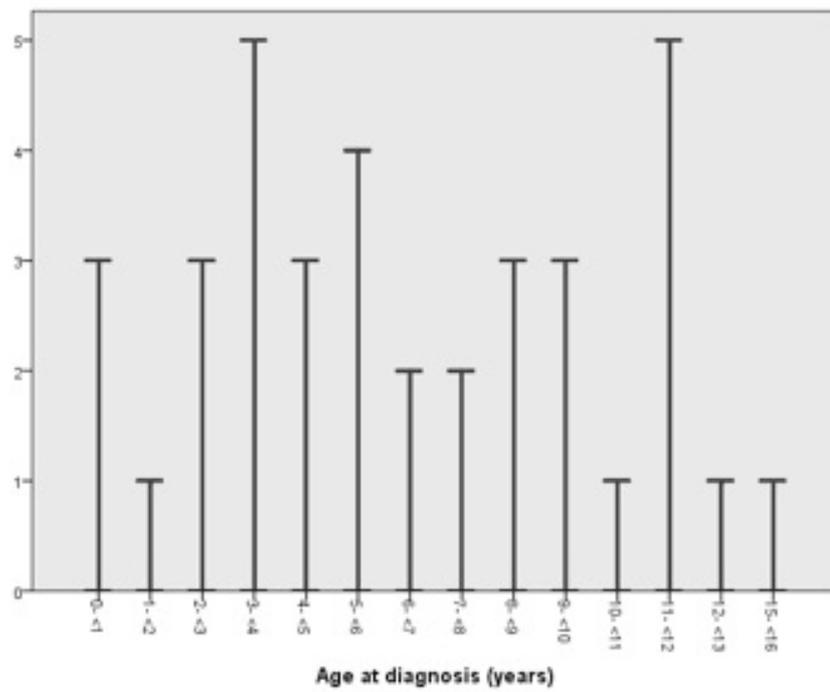
Figure 6. Graph of patients' ages at the time of diagnosis.

Table 7. Features of patients included in this series

Case no.	Age (m)	Gender	F/U time (m)	Death	VolPre (cm³)	VolPost (cm³)	RR	Stage (M0/M+)
P1	7	M	14	Y	24.36	0	0	M+
P2	7	M	52	N	16.33	0	0	M0
P3	10	M	57	N	4.47	0	0	M0
P4	12	M	20	Y	52.85	0.64	0.01	M0
P5	24	M	55	N	71.99	0	0	M0
P6	29	M	29	Y	45.55	0	0	M0
P7	34	M	13	Y	45.23	11.77	0.26	M0
P8	37	F	49	N	36.33	0.41	0.01	M0
P9	39	M	10	Y	17.83	0	0	M+
P10	40	M	14	Y	57.71	9.77	0.17	M0
P11	41	M	9	Y	46.2	10.6	0.23	M+
P12	42	M	14	Y	45.44	9.64	0.21	M+
P13	49	F	63	N	22.04	11.47	0.52	M0
P14	50	M	6	Y	9.47	1.3	0.14	M+
P15	53	F	57	N	24.31	0	0	M+
P16	61	M	12	Y	42.95	3.37	0.08	M+
P17	62	M	10	Y	24.36	0.48	0.02	M0
P18	66	M	63	N	26.47	4.48	0.17	M0
P19	67	M	16	Y	13.32	0	0	M+
P20	80	M	36	N	29.44	0.99	0.03	M+
P21	83	F	86	N	41.92	1.03	0.02	M0
P22	84	F	38	N	34.51	1.41	0.04	M0
P23	86	F	104	N	38.83	6.84	0.18	M+
P24	98	M	55	N	22.54	0	0	M0
P25	101	F	25	Y	31.34	23.27	0.74	M0
P26	103	F	114	N	24.06	8.72	0.36	M0
P27	110	M	45	N	20.92	1.88	0.09	M0
P28	112	M	97	N	55.6	0	0	M0
P29	112	M	81	N	12.32	0	0	M0
P30	125	M	117	N	16.62	0	0	M+
P31	132	M	17	Y	19.4	0	0	M0
P32	132	M	55	N	30.61	0	0	M0
P33	141	F	55	N	46.87	5.23	0.11	M0
P34	142	F	48	N	4.53	0.65	0.14	M0
P35	143	M	48	N	41.6	1.01	0.02	M0
P36	152	M	63	N	50.98	5.35	0.1	M0
P37	181	F	24	Y	34.53	1.85	0.05	M+

M: male, F: female, m: month, F/U: follow up Y: yes, N: no, VolPre: Pre-operative tumour volume,

VolPost: Post operative tumour volume, RR: residuum ratio, M0: absent metastatic disease at

presentation, M+: present metastatic disease (M1-M4).

3.2. Symptoms

Information on symptoms and clinical signs was available in 94% of 37 studied patients. Patients presented with vomiting (73%), headache (62%), ataxia/ataxic gait (43%), sleepiness (14%), loss of weight (14%), reduced appetite (11%), diplopia (11%), change of personality (8%), torticollis (5%), blurred vision (5%), increased head size (5%) and irritability (3%).

The symptoms present prior to diagnosis lasted from 1 day to 43 weeks (mean: 9.4 weeks, SD: 9.7). Data of duration of symptomatology were available in 33 (89%) of 37 cases.

3.3. Signs

Neurological signs at time of presentation included: ataxia/ataxic gait (49%), papilledema (46%), cranial nerve palsy (19%), reduced visual acuity (8%), nystagmus (5%), increased head circumference (5%), torticollis (5%), limitation of upward gaze (3%) and neck stiffness (11%). One of four children aged less than 2 years had a tense anterior fontanel at presentation.

Radiologically proven hydrocephalus was found in 30 patients (81%), 24 of them over the age of 3 years and in 6 patients under the age of 3 years.

3.4. Metastases at diagnosis

A total of 12 (32%) patients had developed metastases at diagnosis. Radiologically proven tumour metastasis was found in 8 (22%) of 37 patients at the time of presentation. Five of those patients (17%) had spinal metastases and three patients had cerebro-spinal metastases. The remaining 4 patients were found to have metastatic disease when medulloblastoma cells were found in the CSF when they underwent diagnostic lumbar punctures. A total of 11 (30%) of 37 patients underwent diagnostic lumbar puncture for staging.

3.5. Surgery

All 37 patients underwent surgery in the form of posterior fossa craniotomy or craniectomy for histological diagnosis and tumour excision.

Histological diagnosis of this series is as follows:

33 (89%) of 37 patients had classic medulloblastoma variant, 2 (5%) patients had desmoplastic medulloblastoma and the other 2 (5%) had anaplastic medulloblastoma.

Postoperative complications occurred in 11 (30%) patients. They included: cranial nerve palsy (16%), hemiparesis (14%), hydrocephalus (14%), intracranial haematoma (8%), CSF leak (8%), mutism (8%), pseudomeningocele (3%) and infection/meningitis (3%).

3.6. Medulloblastoma volume

Medulloblastoma volume was measured in all 37 patients, both preoperatively and in the immediate postoperative period. No patient underwent adjuvant therapy prior to pre- or postoperative MR scans. As such, the measurement of primary and residual medulloblastoma volume was not affected by any form of therapeutic manipulation except the primary surgical tumour excision. Table 7 shows the patients preoperative and postoperative tumour volume (in cm³) and the residuum ratio (postoperative tumour volume / preoperative tumour volume).

The mean preoperative primary medulloblastoma volume was 31.9 cm³ (range: 4.5 cm³ - 71.9 cm³, SD: 15.9 cm³). The mean postoperative residual medulloblastoma volume was 3.3 cm³ (range: 0.0 cm³ - 23.3 cm³, SD: 5.1 cm³), Table 8 and Figure 7. The mean Residuum Ratio (RR) was 0.1007 (range: 0.0 - 0.7, SD: 0.16), Figure 8.

Total primary tumour excision was successfully performed in 14 (38%) of 37 patients as confirmed radiologically. 9 (24%) of 37 patients had residual medulloblastoma volume greater than 15% of the primary medulloblastoma volume. The remaining 14 (38%) patients in this study had residual medulloblastoma volume less than 15% of the primary medulloblastoma volume, Table 9.

Three patients (P13, P25, P26) had exceptionally large residual tumour volume as demonstrated in Table7, Figures 7, 8 and 12. They were all females and had no metastatic disease at the time of diagnosis. They were operated on by different neurosurgeons. In particular:

P13 was 49 months of age and had partial excision of medulloblastoma (RR: 0.52, residuum volume: 11.47 cm³). She suffered a complication with postoperative bilateral extradural haematomas due to pin fixation of the head. She subsequently underwent emergency craniotomy and evacuation of the extradural haematomas. Postoperatively, she had severe ataxia, bulbar palsy

and cerebellar mutism postoperatively. She received craniospinal radiotherapy (55Gy) and completed chemotherapy according to UKCCSG infant PNET Protocol. This patient was alive at 63 months from the time of diagnosis until the end of the study.

P25 was 101 months of age and underwent partial excision of a large cell anaplastic medulloblastoma (RR: 0.74, residuum volume: 23.27 cm³). She developed postoperative hydrocephalus requiring ventriculo-peritoneal shunt insertion. Despite this complication she received craniospinal radiotherapy and chemotherapy but died 25 months after diagnosis due to relapse of her disease.

P26 was 103 months of age and had an uncomplicated subtotal excision of medulloblastoma (RR: 0.36, residuum volume: 8.24 cm³). She had received craniospinal radiotherapy and chemotherapy according to PNET 3 protocol and recurrent PNET protocol respectively. This patient was alive at 114 months from the time of diagnosis until the end of the study.

Table 8. Mean volume of medulloblastoma (37 cases)

VolPre: Pre-operative tumour volume, *VolPost:* Post operative tumour volume and

RR: tumour residuum ratio.

|	Minimum	Maximum	Mean	Median	SD
VolPre cm³	4.47 cm³	71.99 cm³	31.995 cm³	30.61 cm³	15.943
VolPost cm³	0.00 cm³	23.27 cm³	3.301 cm³	0.99 cm³	5.094
RR	0.00	0.74	0.101	0.025	0.159
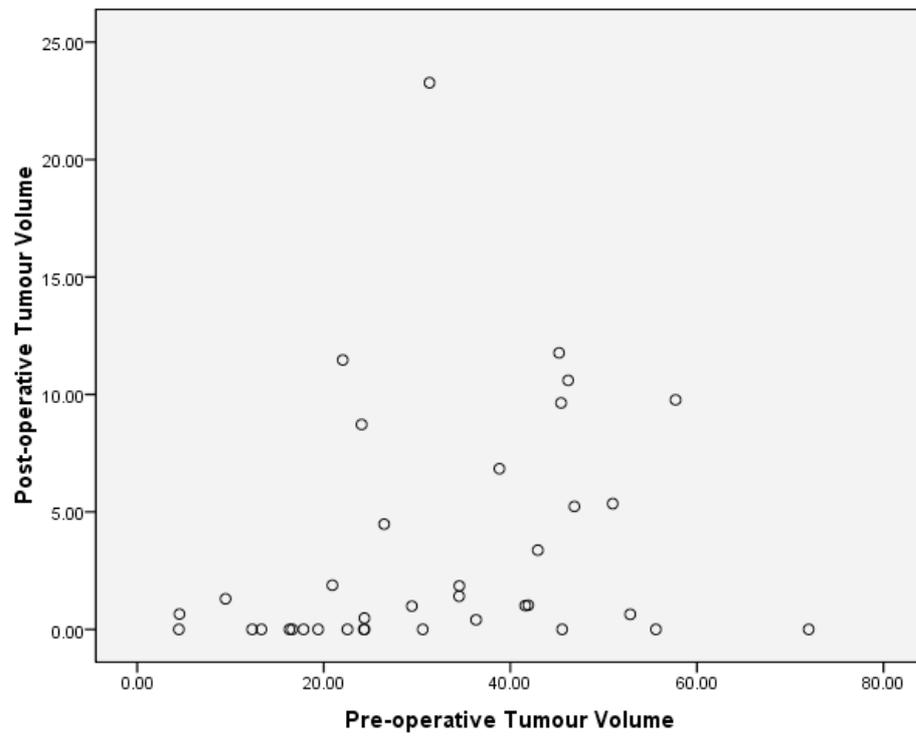
Figure 7. Scatter plot of preoperative and postoperative tumour volume (cm³)
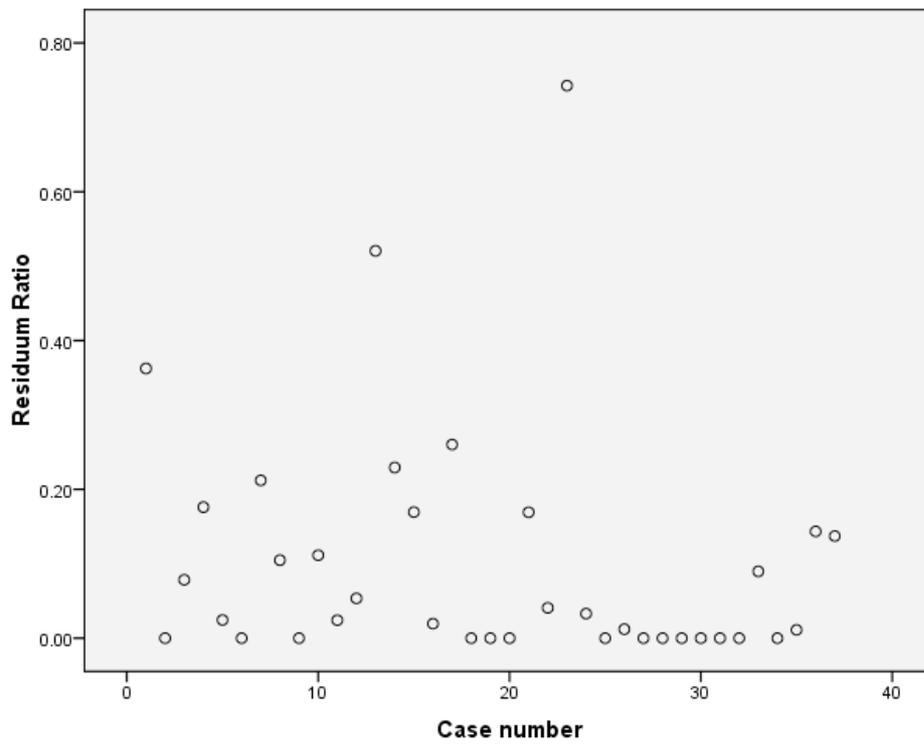
Figure 8. Scatter plot of residuum ratio

Table 9. Patients' tumour residuum ratio (RR)

Case no.	RR>0.15 (more than 15%)	RR<0.15 (less than 15%)
P1		0
P2		0
P3		0
P4		0.01
P5		0
P6		0
P7	0.26	
P8		0.01
P9		0
P10	0.17	
P11	0.23	
P12	0.21	
P13	0.52	
P14		0.14
P15		0
P16		0.08
P17		0.02
P18	0.17	
P19		0
P20		0.03
P21		0.02
P22		0.04
P23	0.18	
P24		0
P25	0.74	
P26	0.36	
P27		0.09
P28		0
P29		0
P30		0
P31		0
P32		0
P33		0.11
PP4		0.14
P35		0.02
P36		0.1
P37		0.05
Total number of cases	9	28

3.7. Radiotherapy

Radiotherapy was administered to 25 patients (68%). Cranio-spinal radiotherapy and booster dose to the posterior cranial fossa was given to 18 patients. 10 of them were treated according the PNET-3 protocol (121;157). 5 patients received Hyperfractionated radiotherapy based on HIT-SIOP PNET 4 protocol (146) and 3 patients were treated according to the POG 9031 protocol (200). 7 patients received only posterior fossa irradiation. In this subset 3 patients received irradiation of 45Gy, 1 patient received 50 Gy, and 3 patients received 55 Gy in accordance with the UKCCSG Infant PNET protocol. All patients who received radiotherapy were more than 3 years of age at the time of commencement of irradiation.

3.8. Chemotherapy

Chemotherapy was administered to all 37 patients in this series. At the end of the study period 14 (38%) patients had completed their chemotherapy whilst 10 (27%) patients were still undergoing treatment. Chemotherapy was discontinued in 13 (35%) patients due to complications or poor tumour response. The chemotherapy regimes used in this study are either currently being used or have previously been used in both national and international

medulloblastoma clinical trials. They are based on the following treatment protocols:

HART-CNS 2001-06 protocol in 3 cases

UK Infant PNET protocol in 5 cases

Packer 's protocol in 3 cases

PNET-3 protocol in 6 cases

PNET-4 protocol in 6 cases

POG 9031 protocol in 4 cases

Recurrent PNET protocol in 4 cases

SFOP Infant Brain Tumour protocol in 6 cases

The protocol of the Hyperfractionated Accelerated Radiotherapy (HART) with chemotherapy for metastatic (M1-3) medulloblastoma CNS 2001 06 protocol consists of vincristine 1.5 mg/m² (maximum 2mg), lomustine 75 mg/m² and cisplatin 70mg/m².

The UK Infant PNET protocol includes:

1. Induction chemotherapy (6 cycles): cyclophosphamide 90 mg/Kg, carboplatin dosed to an AUC of 6.63 mg/ml × min, vincristine 0.05 mg/Kg.

2. Maintenance chemotherapy (4 cycles): vincristine 0.05mg/Kg, lomustine (CCNU) 75 mg/m², cisplatin 70 mg/m².

The Packer protocol includes vincristine 1.5 mg/m² (up to maximum dose of 2 mg), lomustine 75 mg/m², cisplatin 75 mg/m².

The chemotherapy regime of the Recurrent PNET protocol (UKCCSG study CNS 2000 01) consists of cyclophosphamide 4g/m², thiotepa 900mg/m², carboplatin (approximately 550mg/m²).

The POG 9031 protocol consists of:

1. Pre-radiation chemotherapy: cisplatin 90 mg/m² (3 doses on 7 weeks) and etoposide 150mg/m² (6 doses on 7 weeks).

2. Post-radiation chemotherapy (9 cycles): vincristine 1.5 mg/m² and cyclophosphamide 1 g/m²; with 40 Gy craniospinal irradiation.

The SFOP infant brain tumours protocol consist of carboplatin 15 mg/Kg, etoposide 5 mg/Kg/day, vincristine 0.05 mg/Kg, procarbazine 4 mg/kg/day, cisplatin 1 mg/Kg/day, cyclophosphamide 50 mg/Kg.

Data regarding the interval time between primary tumour excision and the commencement of adjuvant treatment was available in 33 (89%) of 37 cases. The mean interval time was 19 days (range: 7 - 53 days, SD: 13, median: 14 days).

Analysis of outcome between tumour volume and radiotherapy or chemotherapy type was not performed due to the small number of cases in each subgroup.

3.9. Outcome

Overall Survival

The overall 5-year survival was 59.5%. All deaths (15 cases, 40.5%) occurred within 29 months from the time of diagnosis as shown in Figure 9. For the subgroup of patients who died the mean survival time was 15.5 months (survival time range: 6 - 29 months, SD: 6.5 months). The cause of death was the relapse of medulloblastoma in all cases. The 5-year survival rate was 52% for BCH patients and 75% for Necker-IGR patients, which was not statistically significant (p= 0.173, log-rank). There was a difference (43%) in the rate of complete tumour excision between BCH and Necker-IGR patients. 6 (24%) of 25 patients of BCH had total excision of medulloblastoma in comparison with 8 (67%) of 12 patients of Necker-IGR. There was also a large difference (36%) in the rate of patients with metastatic disease at the time of diagnosis between BCH and Necker-IGR. 11 (44%) of 25 patients of BCH had metastases at the time of diagnosis in comparison with 1 (8%) of 12

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patients of Necker-IGR. The numbers are too small to determine if these differences in outcome between the two centres are statistically significant.

Survival rates were 50% for males and 82% for females, Table 10. The difference in survival between males and females suggests a trend towards statistical significance (p= 0.061, log-rank), indicating that gender may be a prognostic factor for outcome, Figure 10.

The 5-year survival was 63% (11 of 30 patients died) in patients aged 3 years or more. Patients under 3 years of age at the time of diagnosis had 5-year survival of 43% (4 of 7 patients died). The difference in survival between the two age groups was not statistically significant (p= 0 .45, log-rank), Figure 11.

The 5-year survival of patients with and without metastases at the time of diagnosis was 42% and 68% respectively (p= 0.08, log-rank, Fisher's exact test: 0.16). In addition, 7 (58%) of 12 patients with metastatic disease at the time of diagnosis died. In comparison, 8 (32%) of 25 patients without metastatic disease at the time of diagnosis died.

For *residual ratio cut off 0.15* (residual tumour volume 15% of primary tumour volume), 5 (33%) of 15 patients who died had a RR above 15% and the other 10 (67%) had a RR below 15%. Conversely, for the 22 alive patients

4 (18%) had a RR above 15% and the other 18 (82%) had a RR below 15% (Chi-square: 0.7, Fisher's exact test: 0.43), Figure 12.

The 5-year survival of patients with residual tumour greater and less than 15% of primary medulloblastoma volume was 44.5% and 64% respectively but the difference was not statistically significant (log rank, p= 0.27), Figure 13.
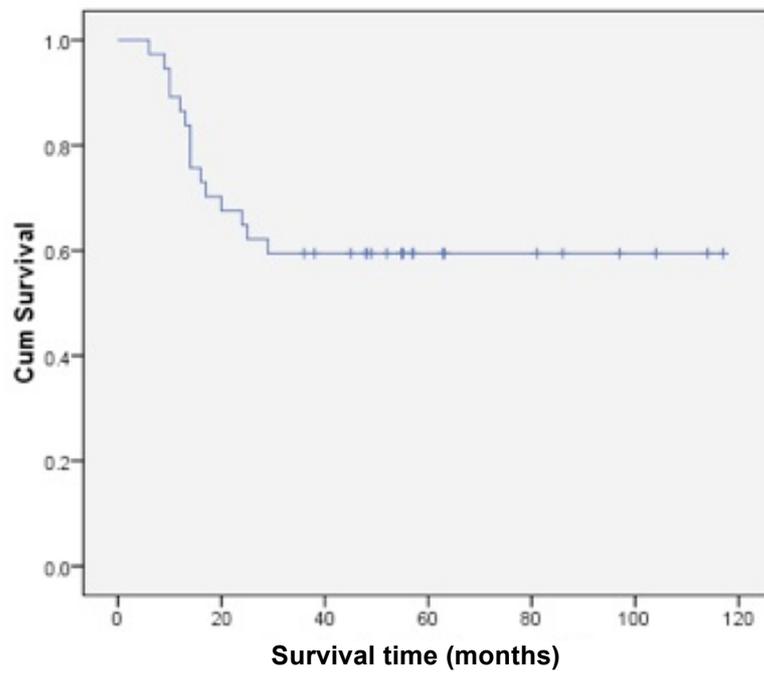
Figure 9. Overall survival in 37 patients.
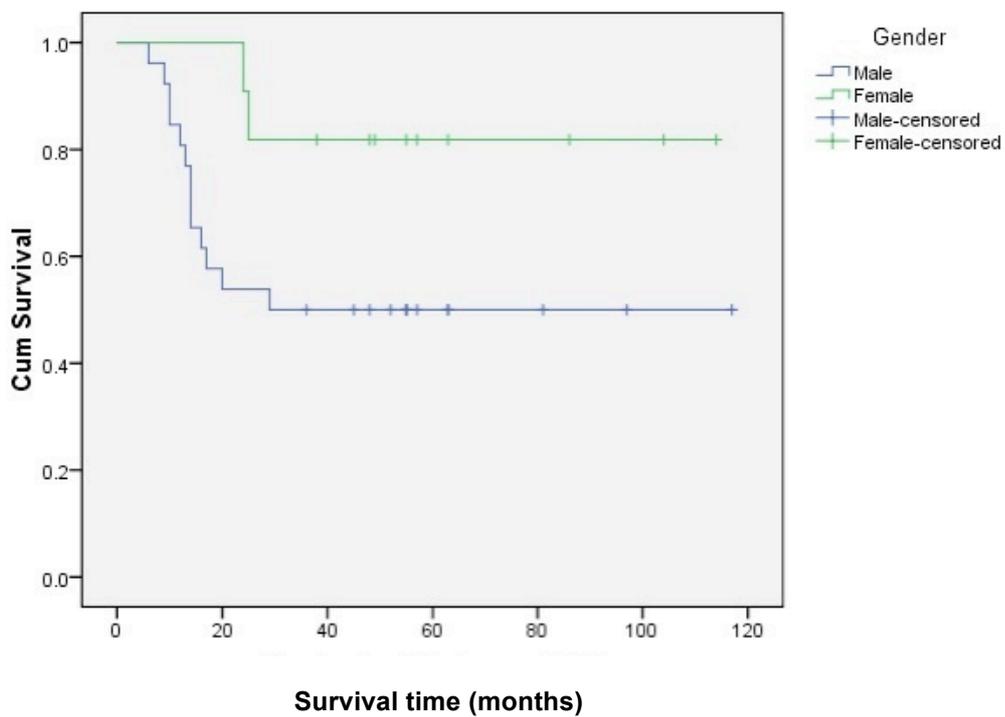
Figure 10. Overall survival classified by gender
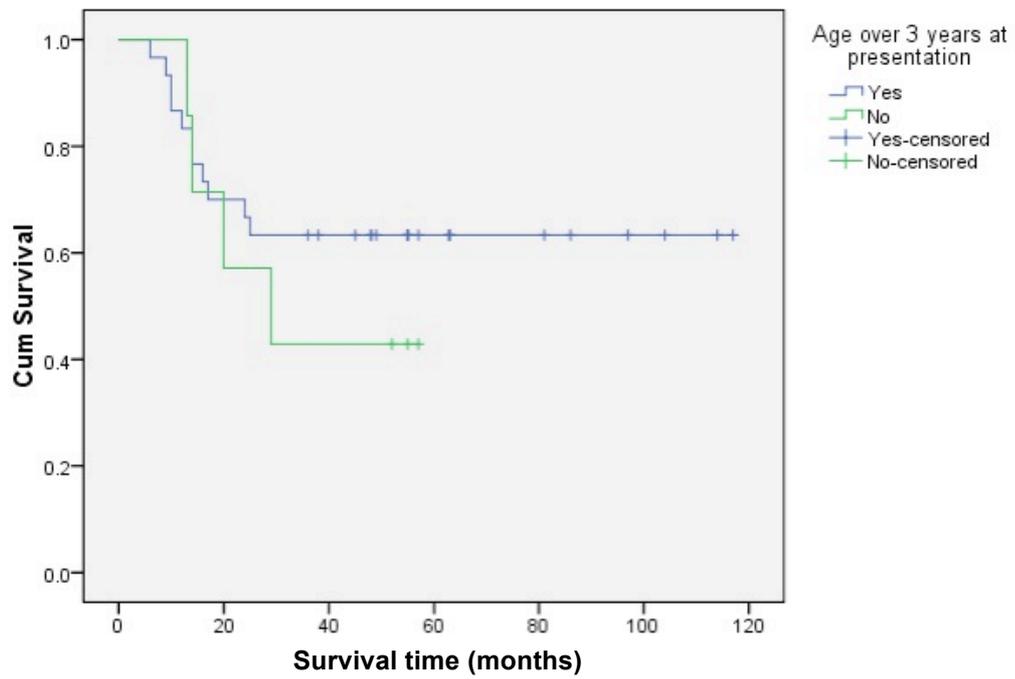
Figure 11. Overall survival in 37 patients classified by the age at the time

of diagnosis of more and less than 3 years.

Table 10. Survival rate by gender

Gender	Number of cases	Dead (%)	Alive (%)
Male	26	13 (50)	13 (50)
Female	11	2 (18)	10 (82)
Overall	37	15 *(40.5)*	22 *(59.5)*
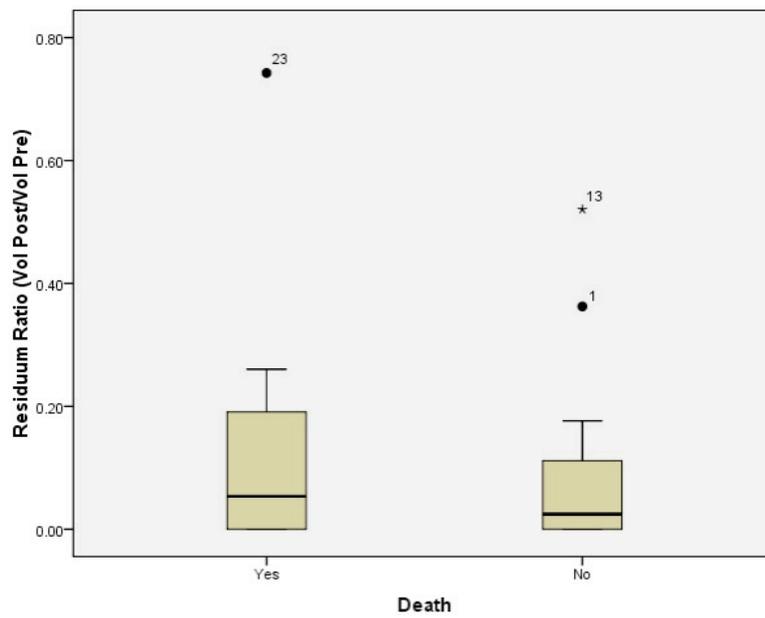
Figure 12. Box plot of mortality and residuum ratio cut off 0.15.

Number 1, 13 and 23 correspond to patients 'number P26, P13 and P25, respectively.
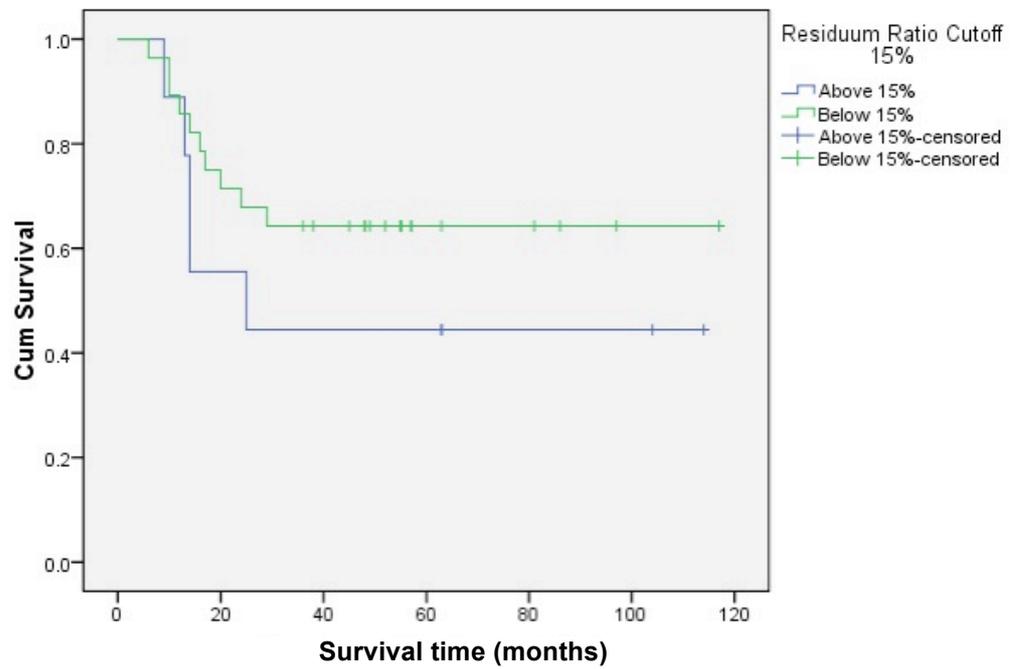
Figure 13. Overall survival in 37 patients classified by the degree of tumour excision of more and less than 15% of primary tumour volume, p= 0.270.

The 5-year survival of patients with residual tumour more and less than 10% of primary medulloblastoma volume was 53.8% and 62.5% respectively but the difference was not statistically significant (log rank, p= 0.505).

The 5-year survival of patients with residual tumour more and less/equal to 1.5 cm³ was 50% and 65.2% respectively but the difference was also not statistically significant (log rank, p= 0.367), Figure 14. 14 (38%) of 37 patients had residual tumour equal or less than 1.5 cm³ and the other 23 (62%) patients had residual tumour more than 1.5 cm³.

8 (35%) of 23 patients with residual tumour equal to or less than 1.5 cm³ and 7 (50%) of 14 patients with residual tumour more than 1.5 cm³ died by the end of the study (Fisher's exact test: 0.493).

It is reported in the literature that the absolute residual tumour burden, which is likely to be in the range of 1 billion cells (1 cm³), is more critical for affective chemotherapy and radiotherapy rather than the percentage of tumour removed (55). Statistical analysis was performed using the value of 1 cm³ of residual medulloblastoma as a cut off in order to find a difference in outcome between patients with residual tumour less or equal to/more than 1 cm³. 5-year survival of patients with residual tumour more than and less/equal to 1 cm³ was 55.6% and 63.2% respectively but the difference was not statistically significant (log rank, p= 0.56).
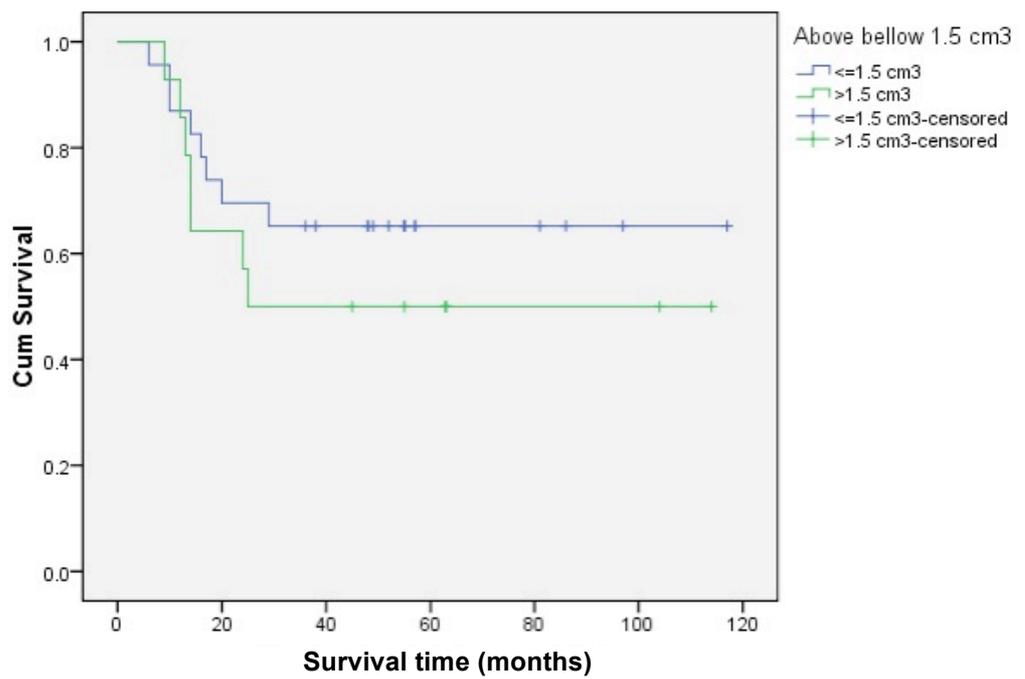
**Figure 14. Overall survival in 37 patients classified by the degree of**

residual tumour volume of more or less / equal to 1.5 cm³,

p= 0.367.

The inability of this study to demonstrate a statistically significant correlation between the extent of primary excision of medulloblastoma and survival prompted further statistical analysis of the data. In particular, an effort was made to find the "ideal" cut off point of residuum ratio or/and the volume of residual tumour which might assist in producing statistically significant results. For that reason histograms, box plot and ROC curve analysis of primary and residual tumour volume with mortality was performed, Figures 15-21.

The mean primary (preoperative) medulloblastoma volume of the deceased and alive patients were 34 cm³ (range: 9.5 - 57.7 cm³, SD: 15.2 cm³, median: 34.5 cm³) and 30.6 cm³ (range: 4.5 - 72 cm³, SD: 16.6 cm³, median: 28 cm³), respectively. The mean residual (postoperative) medulloblastoma volume of the deceased and alive patients were 4.8 cm³ (range: 0 – 23.3 cm³, SD: 6.8 cm³, median: 1.3 cm³) and 2.2 cm³ (range: 0 - 11.5 cm³, SD: 3.3 cm³, median: 0.8 cm³) respectively.
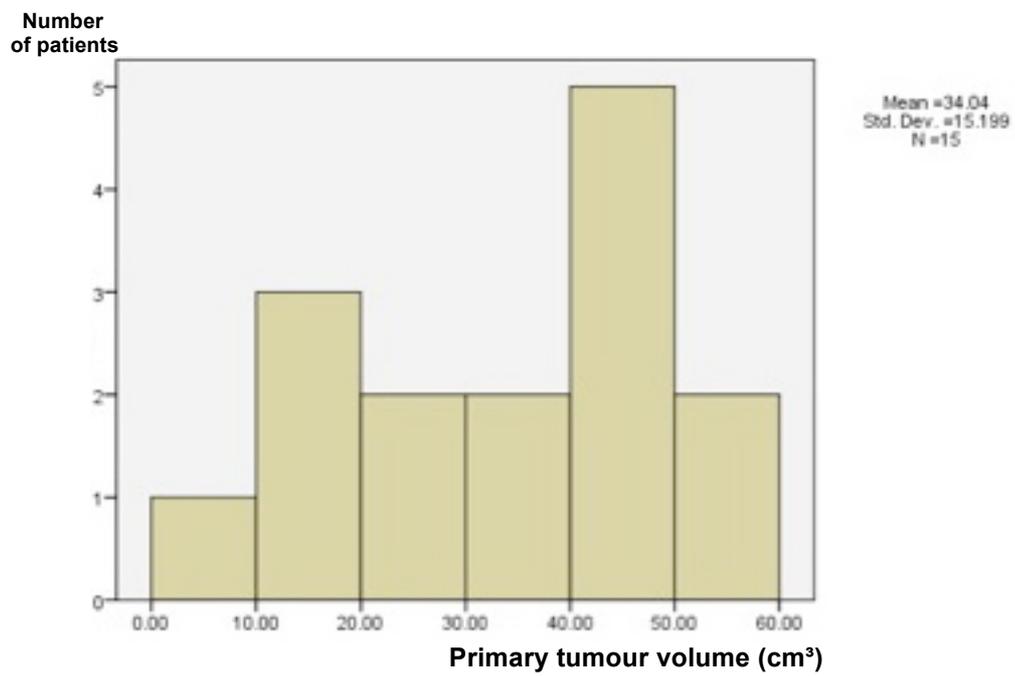
Figure 15. Histogram of primary tumour volume of deceased patients
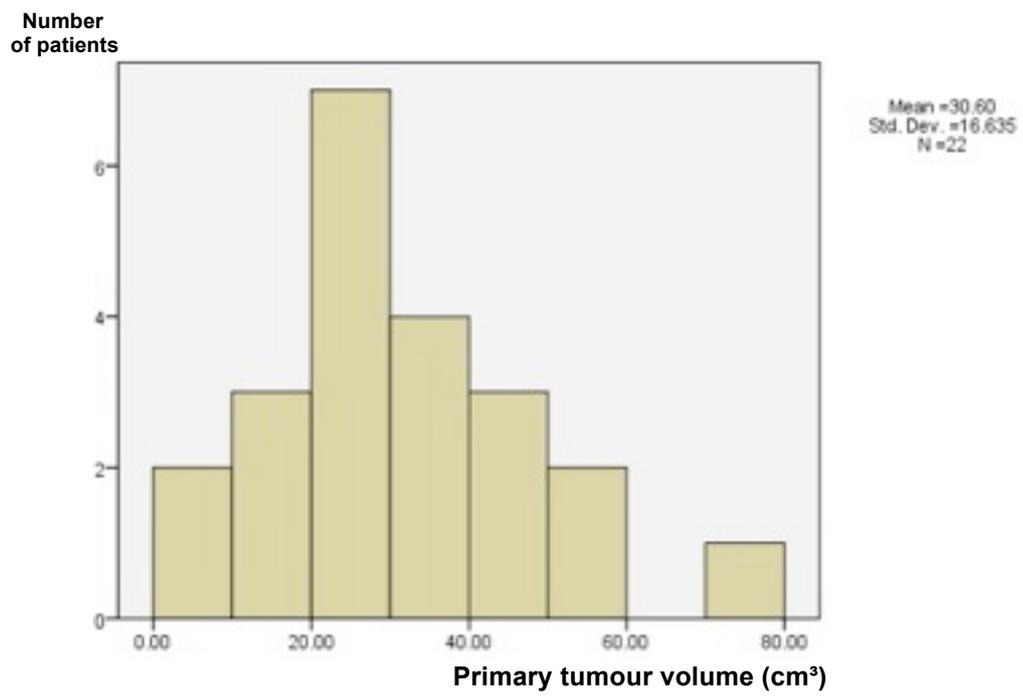
Figure 16. Histogram of primary tumour volume of alive patients

Number of patients

Mean =4.85
Std. Dev. =6.791
N =15

Residual tumour volume (cm³)
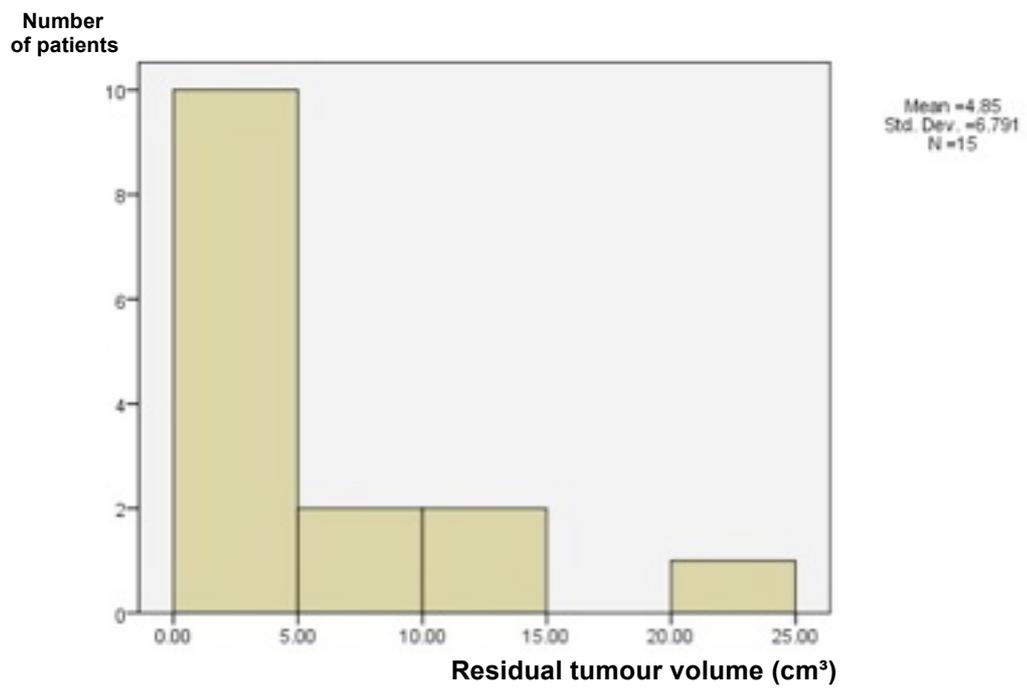
Figure 17. Histogram of residual tumour volume of deceased patients

Number of patients

Mean =2.25
Std. Dev. =3.298
N =22

Residual tumour volume (cm³)
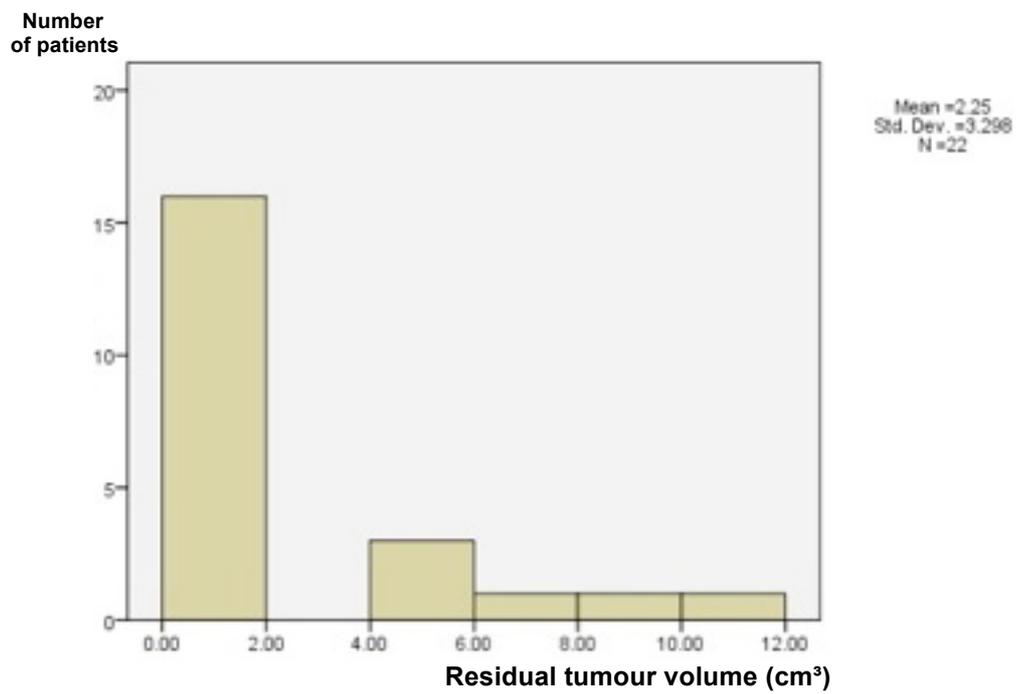
Figure 18. Histogram of residual tumour volume of alive patients
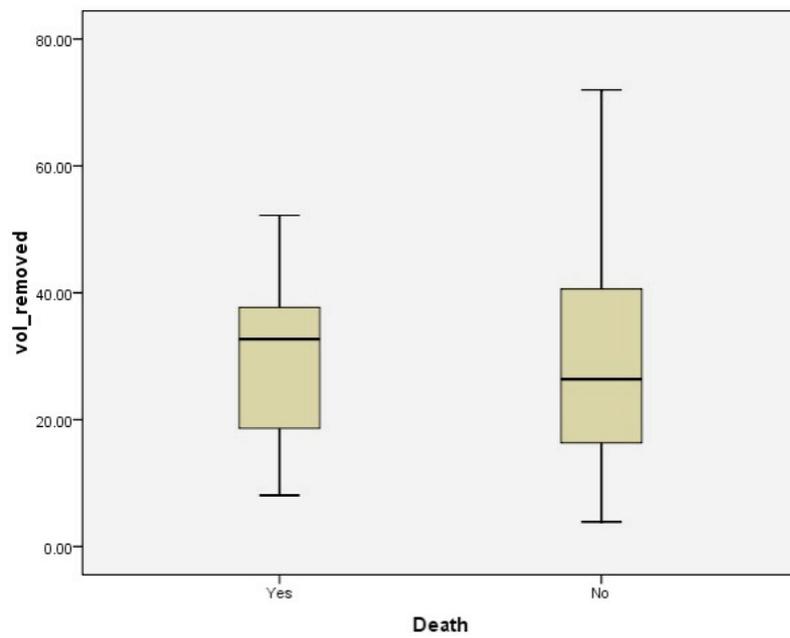
Figure 19. Box plot of removed tumour

volume (cm³) **and mortality.**
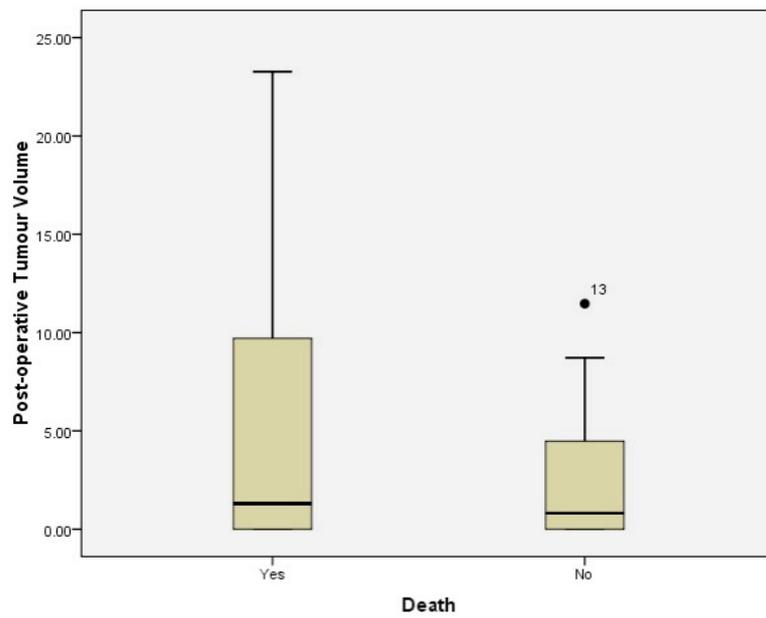
Figure 20. Box plot of residuum (post-operative) tumour

volume (cm³) and mortality.
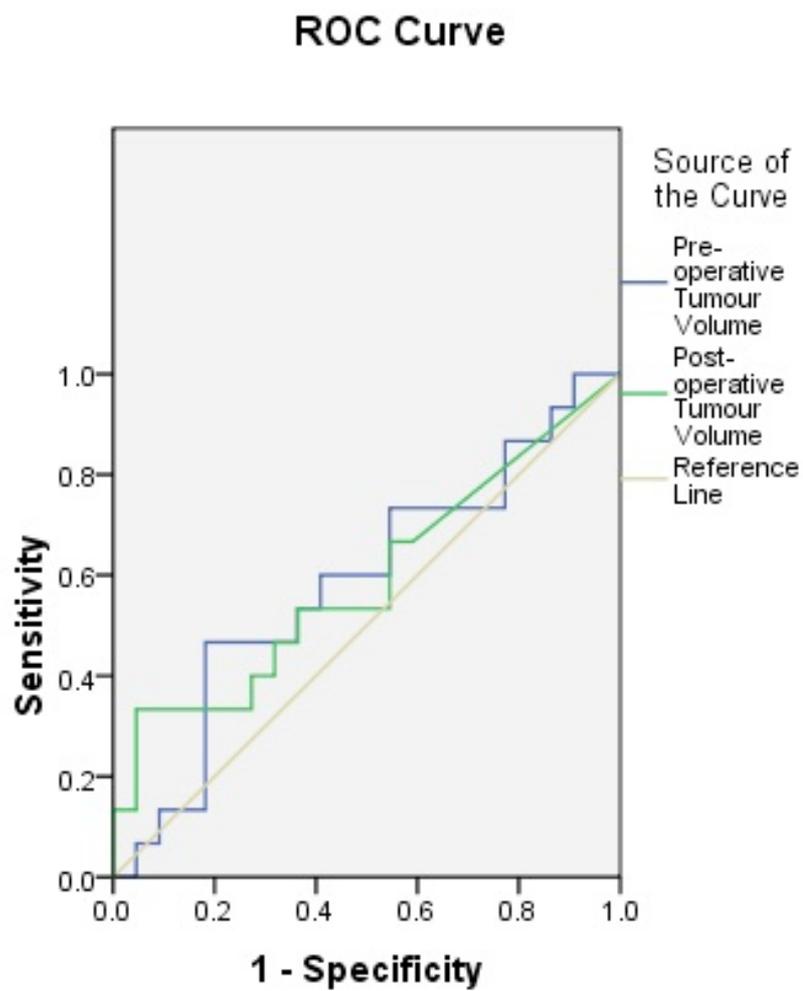
Figure 21. ROC curve of pre- and postoperative (residuum) primary tumour volume.

The above diagrams demonstrate a significant overlap between primary and residual tumour volume distribution in both alive and deceased patients, which compromises the definition of a valuable cut off value.

Furthermore, cox regression analysis of many variables including gender, age, metastatic status at the time of diagnosis, primary tumour volume, residual tumour volume, excised tumour volume and residuum volume cut off was performed. This did not show the residual tumour as an independent prognostic factor of outcome. However, it showed that age (p= 0.02) and metastatic status of patients at the time of diagnosis (p= 0.05) were statistically significant prognostic factors.

In summary, in this series of 37 children (26 males and 11 females) with medulloblastoma, the overall 5-year survival was 59.5%. For those patients who died the mean survival time was 15.5 months (survival time range: 6 - 29 months, SD: 6.5 months). The cause of death was relapse of medulloblastoma in all cases.

The 5-year survival of patients with residual tumour more and less than 15% of primary medulloblastoma volume was 44.5% and 64% respectively but the difference was not statistically significant (p= 0.27). Similarly, the 5-year survival of patients with residual tumour more than and less than 10% of primary medulloblastoma volume was 53.8% and 62.5% respectively (p=

0.505); residual tumour more and less/equal than 1.5 cm³ was 50% and 65.2% respectively (p= 0.367); and residual tumour more and less/equal than 1 cm³ was 55.6% and 63.2% respectively, (p= 0.56).

Chapter 4

4.1. Discussion

One of the greatest challenges in neurosurgical oncology is to achieve complete excision of a brain tumour. In clinical practice, the neurosurgeon strives to achieve complete tumour excision in the safest way possible in order to improve the patient's outcome. However, complete excision of a brain tumour may be associated with significant intra- or postoperative morbidity or mortality. In the event of a subtotal excision of the primary tumour, the neurosurgeon reports the extent of excision as a percentage.

The literature reports a multitude of prognostic factors that contribute to the outcome of children with medulloblastoma, Table 3, (44-46;58) including the amount of residual tumour after primary surgical excision (20;44;46;50;52-55).

Although the importance of primary surgical excision of tumour in patients with medulloblastoma is widely recognised, the true prognostic significance of the extent of surgical resection is still unclear and there is controversy regarding whether less than total excision does (52;55;70;121;195) or does not (48;49) improve patient outcome. In addition, there have not been any studies in the literature which examine pre- and postoperative medulloblastoma volume in relation to outcome. More aggressive surgical resection would

seem a logical approach to improve survival in patients with medulloblastoma (201). A second look operation may also be considered in patients with significant amount of residual tumour after their primary tumour excision.

Many studies have identified the extent of surgical resection as a significant outcome predictor and this has prompted neurosurgeons to attempt complete tumour resection whenever possible (30;50;70;89;198).

Many neurosurgeons use modern technological adjuncts (CUSA, intra-operative MR imaging, neuro-navigation) to achieve complete or near complete surgical excision of primary medulloblastoma in the safest way possible.

Brain shift can occur once the craniotomy has been opened. Intra-operative brain shift results in mis-matching between the anatomical and radiological/neuro-navigational border of the tumour. Subsequently, some neurosurgeons prefer not to use neuro-navigation for guiding the excision of tumour as they consider neuro-navigation to be an unsafe modality. Intraoperative brain imaging aims to reduce the effect of brain shift in order to help neurosurgeon in excision of tumour in a more accurate hence safer way. Also, it helps neurosurgeon to achieve the maximum excision of tumour possible by showing the amount of residual tumour left during surgery. In

general, despite the operative technological advancements surgery still carries a risk of either temporary or permanent neurological deficits (201;202).

It has been reported that there is an increase in the apparent and likely real incidence of posterior fossa mutism which has raised questions about the need for total or near total resections in all patients and whether new neurosurgical techniques, although theoretically safer, might practically increase the morbidity of surgery (99;140).

Postoperative complications and neurological deficits adversely affect quality of life and contribute to a delay in commencing adjuvant therapy. Factors that may potentially correlate with attempts to achieve complete surgical excision of medulloblastoma include the local anatomy (infiltration of brain stem by the tumour), the behaviour of the tumour, the surgical approach used, and the surgeon's competence (146;202).

When dealing specifically with medulloblastoma involving the brain stem, the goal of gross total resection has been controversial because of the potential for surgical morbidity and the absence of data indicating a clear impact on progression-free survival (201;202). Additionally, Evans et al have reported that the extent of surgical resection had no effect on the duration of survival in their cases while controlling for other prognostic factors (48). Packer et al also found no statistical evidence of an association between degree of resection and event-free survival (49). However, other randomized clinical trials (55;88)

have reported that surgical resection of medulloblastoma in children with non-metastatic disease has improved their outcome.

In current clinical practice, in the presence of only local disease, subtotal tumour resection is defined as the presence of tumour of $\geq$ 1.5 cm² on immediate (within 78 hours from operation) postoperative MRI scan (123). The recognition that the clinical outcome of patients with medulloblastoma varies according to age at diagnosis, postoperative tumour residuum and metastatic stage has led to the development of risk-adapted treatment for patients with medulloblastoma (123). At present, average-risk medulloblastoma is treated with maximum surgical resection followed by chemotherapy and whole neuroaxis radiotherapy (96;121;155;158). Although, radiotherapy is a very effective form of treatment for medulloblastoma, it damages the surrounding disease-free brain tissue. In the USA, the standard neuroaxis radiation dose used to treat children with average-risk medulloblastoma has been reduced from 36.0 Gy to 23.4 Gy (123). The concurrent introduction of adjuvant chemotherapy has enabled this reduction in radiation dose to be made without a negative effect on the number of children cured (155;158;199). However a radiation dose of 23.4 Gy is still associated with toxic neurological effects especially in children younger than 8 years, suggesting that there is a need to assess the potential for further reduction of that irradiation dose (123).

The significant role of surgery in the treatment of patients with medulloblastoma has been well recognised since the beginning of the last century as it helps to establish histological diagnosis, relieves compression of brain stem tumour and relieves CSF obstruction at the level of 4th ventricle (obstructive hydrocephalus), all of which are very common occurrences in cases of medulloblastoma. However, the value of aggressive tumour resection has been difficult to analyze until the mid 1990's, because the degree of tumour excision was based on the subjective assessment of individual neurosurgeons (30;48;203;204). Since then, the assessment of the degree of tumour excision and the contribution of residual tumour volume to the outcome of patients with medulloblastoma were based primarily on postoperative CT or MR scans (52;55;89;205).

However, there are no reports in the literature to correlate the volume of residual medulloblastoma with outcome. Although Albright et al found that in children who had both M0 stage of disease and were > 3 years old, the progression-free survival was better in those with <1.5 cm² of residual tumour compared to those with >1.5cm² (p= 0.033), the total volume of residual tumour has remained unknown as only a fraction of the residual tumour was graded based on one slice of CT or MRI scans. The studied CT or MRI slice was that which revealed the larger part of residual tumour (52).

The degree of surgical resection in medulloblastoma has never been assessed volumetrically in the past. This pilot study investigates the correlation between the degree of primary medulloblastoma excision and patient mortality and actuarial survival focusing on the neurosurgical aspect of the management of patients with medulloblastoma. In conducting the power analysis of this study three major issues were considered:

1) The absence of any relevant volumetric study which would help in calculating the required number of patients for recruitment.

2) The low incidence of medulloblastoma i.e. approximately six cases of medulloblastoma were operated per year in BCH (catchment area of 5.5 million people).

3) Number of patients required for this pilot study to satisfy the scientific standards and to be practically achievable.

The above factors resulted in the acceptance of 50% as a value of minimum required difference in survival between the subgroups of the study in order to detect statistically significant results. There was however no relevant information in the literature that would consider the above value as unacceptable for this pilot study.

It seems obvious to only include patients with non-metastatic disease in the study. However, oncologic surgical practice dictates that neurosurgeons remove as much tumour as they can safely, regardless of age or M stage. Although the benefit of resection has only been statistically confirmed in children older than 3 years with M0 stage, resection may well have a clinically important, if not statistically significant role (52). In addition, many of the patients do not have complete MRI of whole craniospinal axis performed preoperatively. In those cases, neurosurgeons did not know if the patients did or did not have metastatic disease at the time of operation. This information would have guided them to strive for total excision of medulloblastoma in children without metastases. Also, for the patients with metastatic disease at the time of diagnosis, it remains unknown if the primary medulloblastoma tumour is genetically identical to cerebral or spinal metastatic tissue. In the event that primary and metastatic tissue are genetically different, their response to future adjuvant therapy may also differ. Which tumour tissue will respond better to adjuvant treatment? The answer to this question would guide neurosurgeons in deciding on the extent of surgical excision.

In this study, more than one third of patients had total tumour resection and another one third of patients had more than 90% excision of primary tumour. In three cases (case number: P13, P25, P26) the residual tumour was more than 30% of the primary tumour volume. As it is demonstrated in Figures 7, 8

and 12, the residuum ratio of P13, P25 and P26 was 0.52, 0.74 and 0.36, respectively. Those RR values are unusually high in comparison to the main group of the patients. A more likely explanation is that the neurosurgeons faced technical difficulties in these particular cases or/and their operative performance was not high enough to achieve better degree of tumour excision on that operating day. Figure 7 shows that the residual tumour volume of P25 was 23.27 cm³ (74% of primary tumour volume). That value is very high and further study of patient outcome was performed after excluding it. In that case, the mean RR was 0.083 (range: 0 – 0.52, SD: 0.12), which is 0.07 less than the original RR value (RR: 0.1, range: 0.0 - 0.7, SD: 0.16). The mean preoperative primary medulloblastoma volume was 32 cm³ (range: 4.5 cm³ - 71.9 cm³, SD: 16.2 cm³). The mean postoperative residual medulloblastoma volume was 2.8 cm³ (range: 0.0 cm³ - 11.8 cm³, SD: 3.9 cm³). Furthermore, the overall 5-year survival was 61.1% for the group of the 36 patients (P25 is not included). In this case there is a 0.6% difference in 5-year survival between those two patients' groups (5-year survival of 37 patients group was 59.5%) which remains insignificant.

Interestingly, 2 (P13 and P26) of those 3 patients were still alive at the latest follow up (63 and 114 months respectively). This might be explained by the fact that they did not present with metastatic disease. In addition, their adjuvant treatment it is possible that had cured the local disease, resulting in the elimination of the limited surgical excision of tumour as a factor

contributing adversely to survival. These cases have uncommonly large volumes of residual tumour. They were included in this statistical analysis as this reflects the variation of the disease in clinical practice, which poses challenges to the medical team.

The overall 5 year survival was 59.5% which is in keeping with the reported outcome of patients with medulloblastoma in different clinical trials (55;96;121;157;206;207). This study did not show a statistically significant difference in 5-year survival (p= 0.27) between the patients with residual tumour less and more than 15% of the primary tumour volume. Also, it did not show a statistically significant difference in survival between the patients with a residual tumour volume more than and equal to or less than 1 cm³ (p= 0.56) and 1.5 cm³ (p= 0.367).

The reasons for that may be the relatively small number of patients in this series. A further reason might be the significant overlapping between the primary and residual tumour volume distribution (ROC curve) in both alive and deceased patients, which compromised the definition of a valuable cut off limit, Figure 21.

It has remained challenging to change the use of the historical value of 1.5 cm² of residual medulloblastoma as a risk factor for patient outcome.

However, Rutkowski et al reported that they stratified patients who were included in HIT-SKK '92 trial based on presence or not of residual tumour and the stage of metastatic disease independently from the size of residual tumour (89). In the same year (2005) Grill et al reported that they stratified patients based on presence of residual tumour and metastasis at diagnosis in the SFOP prospective trial in young children (88).

Grill et al introduced a new risk stratification that was based not only on radiological assessment but also on the surgeon's report. Interestingly, they found from a series of 79 cases that 18 children with non-metastatic disease had a discrepancy between the operative report and the results of early postoperative imaging. In five patients, the neurosurgeon regarded the operation as gross total resection but residual disease was detected on the radiological films; and in 13 patients, no residual disease was found on early CT or MRI scans, whereas the neurosurgeon had reported macroscopic residuum (88).

4.1.1. Study limitations

One of the main limitations of this study is the relatively small number of its patients. It was extremely difficult to recruit a larger number of patients because of:

1) Rarity of the tumour

2) The fact that not all patients with medulloblastoma had pre- and immediate postoperative MRI of craniospinal axis in that period of time (1999-2006)

3) Unavailability of DICOM data of MRI scans in many cases because patients had preoperative MRI scan in district general hospitals or in private hospitals.

Every effort was made to avoid bias in this study. The outcome of the medulloblastoma, i.e. death, relapse or survival without event was not known at the time of selection of patients. The biggest limitation (small number of patients) of this study is mainly due to the rarity of the tumour.

It should be stated that patients who only had postoperative imaging were not studied because it was impossible to calculate the RR as the primary tumour volume was unknown. In these cases, the exclusion of the patients from the study due to absence of preoperative MR scan may have affected the results of the current study as those patients may have smaller or larger residual volume compared with those of studied patients. This also resulted in the exclusion of a number of patients where the absolute value (not the RR) of their residual

tumour volume could be correlated with their outcome. The data from these patients could be used in a future study.

A significant number of patients with medulloblastoma were not included in the study (Chart 1) because their pre- and postoperative MR scans were not available in DICOM form due to administrative reasons (loss of optic discs on which MR scan data was stored, discard of original MR scanners, incompatibility between the original optic discs and the available MR scanner hardware). These factors resulted in the exclusion of a group of patients with potentially different pre- and/or postoperative tumour volumes and RR compared to patients of the current series. Subsequently, the current series of patients may not be representative of the whole population of patients with medulloblastoma.

In addition, there are other sources of bias as follows:

1) The technical limitations of MR scanners affect the quality of obtained MR images of the tumours. In particular, the studied images were produced by 1.5 Tesla MR scanners, which are inferior to 3 Tesla MR scanners from the radiological point of view.

2) The quality of tumour enhancement may be affected by the type of contrast media and the modality of intravenous administration such as contrast media

infusion rate, amount of the contrast media, interval time between the injection of the contrast media and MR scanning. Subsequently, there may be some radiological / imaging bias between pre- and post operative MR scans as the study series patients have not been scanned in the same MR scanner, by the same radiographer, and by using the same contrast media.

3) The genetic profile of medulloblastoma may be different between patients, and may affect outcome, but this information was not known.

4) A lumbar puncture has not been performed in all patients as it was not part of the routine clinical practice during that period of time (1999-2006). Subsequently, there is a high possibility that patients with M1 stage to had been mistakenly classified as M0 stage. That is a diagnostic bias and may have resulted in the undertreatment of some patients.

5) Adjuvant treatment (chemotherapy and radiotherapy) was not identical in all patients i.e. chemotherapy or radiotherapy protocols, radiotherapy devices, medical or nursing teams (treatment bias).

6) The absence of any calculation of the volume of metastatic disease affects the value of the total postoperative tumour volume. However, the calculation of the volume of metastases is challenging for the "icing sugar" type of leptomeningeal metastases due to its extremely small size.

All of the above factors may affect the accuracy of diagnosis, the effectiveness of patients treatment and outcome but they could not be controlled for this study.

4.1.2. Future directions

Further studies into the role of volumetrically assessed residual tumour as a risk factor of clinical outcome of children with medulloblastoma will require a large number of patients. For example, for a Type I / alpha (α) error with an alpha value of 0.05, and for Type II / beta (β) error with beta value of 0.2 and powered at 80%, the minimum sample required for each group would be 163 patients in order to detect a minimum difference of 15% in survival (Hazard ratio: 1.51). This pilot study has shown that 24% (approximately 1:4 patients) of patients in this series had residual tumour volume more than 15% of the primary tumour volume. It would therefore require an international multicentre trial in order to recruit 652 cases in order to obtain a group of 163 patients with residual tumour of more than 15% of the primary tumour volume.

Many prognostic factors have been reported in the literature that affect patient outcome (Table 3). Ideally, a further study about the correlation of volume of residual tumour and patient outcome should include patients with absence of

metastatic disease matched for prognostic factors such as age group (less or more than 3 years), gender, histological variant, genetic profile, and medical treatment (chemotherapy or/and radiotherapy).

This study suggests that MR image analysis with segmentation technique could feasibly be used in future medulloblastoma trials in order to volumetrically assess the volume of primary and residual tumour and correlate them with:

1) Incidence of postoperative mutism.

2) Neuropsychological consequences of tumour excision.

3) Time to tumour relapse.

4.2. Conclusion

1. This study has demonstrated the feasibility of performing volumetric analysis of residual tumour volume in a multi-centre study.

2. Whilst this study has shown that there is a trend for patients with less residual tumour volume to have better outcome than those with more residual tumour volume (Figure 13 and 14), that trend was not statistically significant.

The number of the patients in this pilot study was not large enough to reach a conclusion regarding the correlation between the tumour volume of childhood medulloblastomas and patient outcome.

3. This study has however provided the power calculation for the minimum number of patients required in a further study in order to produce statistically significant result. This question can also be prospectively included in future therapeutic clinical trials.

Peer- Reviewed Publication

1. Kombogiorgas D, Sgouros S, Walsh AR, Hockley AD, Stevens M, Grundy R, Peet A, English M, Spooner D. Outcome of children with posterior fossa medulloblastoma: a single institution experience over the decade 1994-2003. **Childs Nerv Syst. 2007 Apr;23(4):399-405.**

2. Peet AC, Davies NP, Ridley L, Brundler MA, Kombogiorgas D, Lateef S, Natarajan K, Sgouros S, MacPherson L, Grundy RG. Magnetic resonance spectroscopy suggests key differences in the metastatic behaviour of medulloblastoma. **Eur J Cancer. 2007 Apr;43(6):1037-44.**

3. Kombogiorgas D, Natarajan K, Sgouros S. Predictive value of preoperative ventricular volume on the need for permanent hydrocephalus treatment immediately after resection of posterior fossa medulloblastomas in children. **J Neurosurg Pediatrics. 2008 Jun;1(6):451-5.**

4. Kombogiorgas D, Puget S, Boddaert N, Peet A, English M, Natarajan K, Grill J, Couanet D, Sainte-Rose C, Sgouros S. Correlation of Residual Tumour Volume with Survival in Children with Medulloblastoma. Abstract. **Childs Nerv Syst 2008;24:660.**

Anticipated Publications

1. <u>Kombogiorgas D</u> [1], Puget S [2], Boddaert N [2], Peet A [1], English M [1], Natarajan K [1], Grill J [3], Couanet D [3], Sainte-Rose C [2], Sgouros S [1]. Correlation of immediate primary postoperative residual tumour volume with survival in children with medulloblastoma.

Birmingham Children's Hospital, Birmingham, U.K [1]. Hôpital Necker-Enfants Malades, Paris, France [2]. Institute Gustave Roussy, Paris, France [3].
In preparation.

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