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Included in this document:

a) Abstract
b) Manuscript
c) Letter of acceptance

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Sequential improvement in paediatric medulloblastoma outcomes in a low-and-middle-income country setting over three decades

Twitter statement:

Sequential improvement in paediatric medulloblastoma outcomes in a LMIC setting over 3 decades

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Short running title: Paediatric medulloblastoma in low-and-middle-income countries

Keywords: Paediatric brain tumours; medulloblastoma (MB); radiotherapy (RT); 3D conformal radiotherapy (3DCRT); craniospinal irradiation (CSI); chemotherapy; paediatric neurosurgery; leptomeningeal spread (LMS); cerebrospinal fluid (CSF); paediatric oncology; low-and-middle-income countries (LMIC); Paediatric Oncology in Developing Countries (PODC); overall survival (OS)

Abstract

Background: Medulloblastoma (MB) is the commonest malignant brain tumour of childhood. Accurate clinical data for paediatric MB in the LMIC setting is lacking. Sequential improvements in outcome seen in high income countries are yet to be reflected in LMIC.

Aim: Quantification of paediatric MB outcomes in the LMIC setting over three decades of advances in multidisciplinary intervention.

Setting: Cape Town, South Africa

Methods: This was a retrospective study of 136 children with MB diagnosed between 1985 and 2015. Modified Chang criteria were used for risk stratification. The primary study objective was overall survival (OS), quantified by analysis of epidemiological, clinical and pathological data.

Results: OS improved significantly during the most recent decade (2005-2015) when compared with the preceding two decades (1985-1995 and 1995-2005). Despite reduced dose craniospinal irradiation for standard risk cases, OS was significantly greater than during the preceding two decades. High-risk disease was identified in 71.4% of cases and was associated with significantly inferior OS compared with standard risk cases. Improved OS was positively correlated with therapeutic era, 3-D conformal radiotherapy technique, older age at diagnosis, classic and desmoplastic histology, extent of resection and absence of leptomeningeal spread on imaging.

Conclusion: Advances in multidisciplinary management of MB in our combined service are associated with improved survival. Access to improved imaging modalities, advances in surgical techniques, increased number of patients receiving risk-adapted combination chemo- and/or radiotherapy as well as craniospinal irradiation using a linear accelerator with 3D planning, are considered as contributing factors.

Introduction

Brain and central nervous tumours in children are rare but result in mortality and morbidity that is disproportionate to incidence rates. They constitute the leading cause of paediatric cancer-associated deaths worldwide, despite lower incidence rates in comparison with haematological malignancies[1].

A recent report analysing paediatric cancer survival rates in two South African tertiary hospitals, revealed that brain tumours represent 19.5% of all childhood cancers diagnosed, second only to leukaemia constituting 25% of cases. Consistent with international reports, those with brain tumours exhibited the lowest survival rate with a median survival time of 18 months compared to 47 months for leukaemia cases[1,2].

Medulloblastoma (MB) is the most common malignant paediatric brain tumour. MB comprise a group of histologically and molecularly diverse posterior fossa tumours, pathologically described as undifferentiated, small round blue cells with mild to moderate nuclear pleomorphism and high mitotic counts. These tumours are of embryonal origin and are thought to originate from progenitor cell lineages present during early brain development. Four histological variants exist: classic, desmoplastic/nodular, MB with extensive nodularity (MBEN) and anaplastic/large-cell (LCA). In addition, four molecular subgroups including wingless (WNT), sonic hedgehog (SHH), Group 3 and Group 4 have been identified[3-7]. Molecular subgrouping may influence treatment decision-making and is a strong predictor of prognostic outcomes[5,8,9].

Approximately 20% of paediatric brain tumours in high income countries (HIC) are MB. Data from LMIC exhibit substantial variation in incidence ranging between 6-50%[10-14]. The exact epidemiological, clinicopathological characteristics and survival outcomes of MB within South-Africa's markedly heterogeneous population are unknown. Risk stratification of children with MB using the modified Chang system allows for identification of standard and high-risk groups[15]. Standard risk is defined as all of the following: age 3 years or more at presentation, less than 1.5cm^2 residual tumour after resection, CSF negative for tumour cells, absence of leptomeningeal spread on CT/MRI and classic or desmoplastic histology. High-risk disease is defined when any of the following are present: Age less than 3 years, residual tumour of more than 1.5cm^2 after surgery, CSF positive for tumour cells, leptomeningeal spread on CT/MRI or LCA histology[15,16]. Over the last decade advances in multidisciplinary management of patients with MB in HIC have resulted in 5-year OS rates of 80-85% for standard risk and 65-70% for high-risk disease[16,17]. This improvement is not apparent in LMIC and may be attributed to common constraints such as delayed/inaccurate diagnoses with advanced disease at presentation, high rates of hospital acquired infections following neurosurgical intervention, and co-morbid illness such as HIV, TB, parasitic disease and malnutrition.

Limited access to radiotherapy services with significant delays from referral to point of treatment, as well as the ever-expanding limitations within socio-economic support structures further hamper optimal care[11,18,19].

To quantify treatment outcomes associated with MB in the context of a LMIC, we undertook a 30-year review of all children (aged 0-15), who between 1985 and 2015, were diagnosed with MB. They underwent multidisciplinary management at the Red Cross War Memorial and Groote Schuur Hospital complex. Demographic and clinicopathological characteristics were recorded and related to OS.

Methods

Cohort and clinical data

A 30-year retrospective comparative assessment of 136 patients with MB, aged between 0-15, treated at Red Cross War Memorial and Groote Schuur Hospital complex (single institution) between 1985 and 2015 was performed. Information obtained from oncology, neurosurgery and radiotherapy (RT) patient records was cross-referenced to maximise data capture and ensure accuracy. Information retrieved included age, sex, date of birth, date of diagnosis, presenting clinical features, histology, radiology reports, extent of resection, CSF analysis, chemotherapy and/or RT schedules. CSF obtained were either intraoperative cisternal puncture or day 14 post-operative lumbar puncture samples. Due to the duration of this study and associated constraints of missing patient records, we were unable to accurately ascertain the original source of CSF fluid. These limitations also resulted in numbers for the respective subgroups not equating to the total population number of 136. Missing data is therefore included in the data tables. Furthermore, it was impossible to assess quality of survival which ultimately constitutes the rationale for improved stratification and treatments. Laboratory results were obtained from printed copies in the patient record or from accessing the South African National Health Laboratory Service DisaLab (up to July 2013) or TrakCare (August 2013 to end of 2015) platforms. Imaging results were obtained from printed radiology reports, clinical notes and accessing iSite Enterprise Radiology PACS. Prior to 1992 only CT scans were available. Between 1992 and 2001 patients received CT scans at Red Cross War Memorial Hospital and MRI scans at the local Medical Research Council facility. Between 2001 and 2009 MRI scans were performed at Groote Schuur Hospital. An MRI scanner was introduced at Red Cross War Memorial Hospital in 2009. Prior to 2012 contrasted CT was used to evaluate for leptomeningeal spread during the initial diagnostic assessment. During the latter part of this study MRI was predominantly used. Over time, immediate postoperative MRI was used to determine surgical outcomes. Using the modified Chang criteria, cases were stratified into standard and high-risk groups[15].

The combined data was further cross-referenced with the South African Children's Cancer Study Group (SACCSG) registry. Ethics approval was obtained from the Human Research Ethics Committee, University of Cape Town (Reference 777/2018 linked to sub-study 149/2014).

Radiotherapy

During the first two decades (1985–2005) 2D planning in conjunction with a ^{60}Co gamma ray unit radiotherapy was used. From 2005-2015 all cases were 3D planned using 6 MV photon energy and treated on a linear accelerator (Linac). From 2007 standard risk MB was treated with reduced-dose craniospinal irradiation (CSI) consisting of 23.4Gy to the craniospinal axis in 13 fractions together with a tumour bed boost of 30.6-32.4Gy in 17-18 fractions. This is in accordance with the SIOP PODC adapted treatment recommendations[11]. High-risk disease was treated with full dose CSI of 36Gy in 20 fractions with a boost dose of 18-19.8Gy in 10-11 fractions to the tumour bed. Selected cases harbouring significant gross residual disease occasionally necessitated an additional boost depending on dose to surrounding organs at risk.

Extent of Resection

Prior to 2011 contrast-enhanced CT was used for postoperative imaging (usually the day after surgery) and was subsequently replaced by immediate post-operative MRI (<48 hours post-surgery) imaging during the latter part of this study. Gross total resection (GTR) was defined as total resection of the primary tumour without residual lesions as reported by the neurosurgeon and/or post-surgical imaging when available. Near total resection (NTR) was defined as less than 1.5 cm^2 residual tumour, whereas sub-total resection (STR) represented incomplete resection with greater than 1.5 cm^2 residual tumour.

Chemotherapy

Data captured reflects administration of chemotherapy at any point of the patient journey. During the early phases of this study, chemotherapy was not routinely prescribed, except for high-risk cases, most commonly in young children under the age of 3-4, in whom expected long-term sequelae of craniospinal radiotherapy necessitated delay of radiotherapy and the use of alternative treatment modalities. From 1985 to 1995, all high-risk patients received chemotherapy, either because start of CSI was delayed, or adjuvantly, or both, but this was given at Groote Schuur Hospital. In the second

cohort, high-risk patients received adjuvant vincristine, etoposide and cyclophosphamide (VEC) at Red Cross War Memorial Hospital and after 2005, all high-risk patients and patients with standard risk received reduced dose CSI together with concurrent and adjuvant chemotherapy. After 2015 concurrent weekly Vincristine was omitted.

Tissue preparation and immunohistochemistry

Tumour specimens were processed by anatomical pathology as per standard hospital protocol. Histological and phenotypical subtyping was performed using standard procedures as previously described[20].

Statistical analysis

Statistical analysis was performed using GraphPad Prism. Kaplan-Meier methodology was applied to quantify survival outcomes. Log-rank tests were used to determine differences between groups[21]. OS was calculated as time from the date of diagnosis to death from any cause or last contact. Chi-square (χ^2) tests were performed to measure differences between derived proportions. To evaluate the potential influence of each risk constituent on outcome, OS for age, histological subtype, CSF status, leptomeningeal spread and extent of resection was calculated. Univariate Cox regression analysis of OS determinants was performed to quantify confidence intervals and hazard ratios graphically depicted on a Forest plot.

Results

Study Population and Demographics

136 patients who had undergone multidisciplinary management for MB between 1985 and 2015 were identified. Demographic and clinical characteristics are summarised in *Table 1*. The male to female ratio was 0.9 and median age at diagnosis was 2.1 and 7.3 for the 0-3 years group, and 3-15 years groups respectively, with a combined median age of 5.7 years. The standard risk cases were 34/119 (28.6%) of the entire cohort and 85/119 (71.4%) were high-risk, whereas 17 cases could not be accurately staged. Histologically, the evaluable sub-cohort consisted of 93/128 (72.7%) classic histology, 22/128 (17.2%) desmoplastic nodular/MBEN and 13/128 (10.1%) large cell/anaplastic (LCA) variants. Analysis of CSF results indicated that 22/93 (23.7%) cases were positive for

malignant cells. Due to the constraints associated with the duration of this study we were unable to determine the origin of the CSF samples and results reflect either intraoperative cisternal puncture and/or day 14 post-operative lumbar puncture samples. Baseline diagnostic imaging of the spinal axes (either CT or MRI depending on era) at presentation exhibited features consistent with leptomeningeal disease/drop metastases in 18/90 (20.0%) evaluable cases.

Survival Analysis

5-year and 10-year OS for the entire cohort was 60.5% and 54.6% respectively (*Figure 1*). Survival was improved for the most recent era 2005-2015, in comparison with the preceding two decades (Log-rank test p=0.0423*; n=136). The 5-year OS (OS5) for the first, second and third decades was 51.5% (95% CI 39.6-66.6; n=52), 49.3% (95% CI 33.6-64.8; n=35) and 76.2% (95% CI 68.7-84.7; n=49) respectively. The 10-year OS (OS10) for the first, second and third decades was 49.5% (95% CI 23.6-58.5; n=52), 49.1% (95% CI 33.4-63.4; n=35) and 73.2% (95% CI 67.1-89.6; n=49) respectively. OS5 during 2005-2015 was significantly higher compared to 1985-1995 (p=0.0186*) and 1995-2005 (p=0.0319*) when individually compared. No significant difference in OS was observed for 1985-1995 versus 1995-2005 (p=0.5650).

Unequal risk distribution among therapeutic groups can influence survival assessment and interpretation. *Table 2* summarises the prevalence of measurable variables within each group. Decade 2005-2015 was characterised by a significantly greater number of cases with absent leptomeningeal spread (p=0.001**), standard risk disease (p=0.0048**) and GTR (p=0.0310*), whereas STR occurred less frequently (p=0.003**).

Across the entire cohort, standard risk MB was associated with significantly superior OS compared to high-risk disease (*Figure 2a*). OS5 and OS10 rates for standard risk patients were 78.7% (95% CI 64.7-89.7) and 70.4% (95% CI 60.5-88.6) respectively, compared to 51.2% (95% CI 39.6-58.3) and 45.7% (95% CI 33.6-57.2) for high-risk disease (OS5; p=0.0026**; n=117). Incompletely staged cases comprised 19/136 (13.9%).

OS was significantly different between age groups (*Figure 2b*). OS5 and OS10 for age group 0-3 years were 32.5% (95% CI 18.2-51.9) for both decades, compared to age group 3-15 years with OS5 and OS10 of 67.1% (95% CI 54.5-73.8) and 59.8% (95% CI 47.3-70.1) respectively (OS5; p=0.0008***; n=136).

LCA histology was associated with significantly inferior OS compared to classic and desmoplastic variants (p=0.0347*; n=128) (*Figure 2c*). Both OS5 and OS10 were 39.5% (95% CI 20.8-54.9) for

cases with LCA histology. In comparison, classic histology exhibited OS5 and OS10 of 66.1% (95% CI 54.5-74.7) and 60.5% (95% CI 51.2-73.1) respectively, whereas desmoplastic histology was associated with OS5 and OS10 of 58.9% (95% CI 38.5-77.1) and 52.8% (95% CI 30.3-70.6) (p=0.298).

No significant difference in OS was observed for patients with or without malignant cells in CSF samples (p=0.8106; n=93) (*Figure 2d*) however, the presence of leptomeningeal spread on pre-operative diagnostic imaging was associated with reduced survival (*Figure 2e*). OS5 and OS10 in the absence of leptomeningeal spread was 69.7% (95% CI 57.6-78.7) and 64.8% (95% CI 57.3-78.7) respectively. Leptomeningeal spread was associated with OS5 and OS10 of 49.6% (95% CI 33.7-55.4) and 33.9% (95% CI 17.3-52.2) respectively (p=0.0482*; n=90). We were unable to accurately document 46/136 (33.8%) of cases for leptomeningeal involvement.

Maximal safe surgical resection was performed by specialised paediatric neurosurgeons throughout the study period. OS5 and OS10 for GTR cases was 69.6% and 66.5% respectively compared to 55.5 and 49.4% for NTR cases (p=0.2810). OS5 and OS10 for STR cases were 48.4% and 43.8% respectively and was significantly lower than GTR cases (p=0.0343*; n=125) (*Figure 2f*). Of the 136 cases we were unable to ascertain the extent of resection in 11 cases.

Survival was not significantly different between males and females, however a trend towards increased survival was seen for female patients (*Supplemental Figure A)*. OS5 and OS10 for females were 66.8% (95% CI 61.1-72.3) and 61.6% (95% CI 54.7%-67.9%) respectively, compared to males with OS5 and OS10 of 51.7% (95% CI 44.1-59.2) and 48.4% (95% CI 40.7-55.1) (p=0.1070; n=136). Risk stratification and treatment modalities in relation to the male and female sub-cohorts were quantified (*Supplemental Table A*). Classic histology was observed in 55/67 (82.1%) female cases compared to 38/61 (62.3%) males (p=0.0168*; n=128). Only 2/67 (3%) female cases harboured LCA histology, significantly fewer than their male counterparts with 11/61 (18.0%) (p=0.0068*; n=128). No additional differences in relation to sex was observed.

Because of the study duration and resultant missing patient data we could only with certainty evaluate radiotherapy outcomes in 100/136 (73.5%) of patients. Of these 44/100 (44%), 21/100 (21%) and 35/100 (35%) were treated during the first, second and third decades, respectively. Fractionation and dose prescriptions are summarised in *Table 3.* Linac-based 3D conformal RT (3DCRT), employed during the 2005-2015 era, was associated with OS5 and OS10 rates of 76.2% and 73.2% respectively. The combined OS5 and OS10 during the preceding two decades, when 2D Cobalt-60 based RT was used, were 59.4% and 57.8% respectively (p=0.0286*; n=100) (*Figure 3).*

Surgical outcomes were evaluable in 125/136 (91.9%; n=125) of cases. The number of GTR achieved during 2005-2015 was 23/45 (51%), significantly higher compared to the 16/47 (34%) and 10/33 (30%) during 1985-1995 and 1995-2005 respectively (p=0.0310*). Significantly fewer STR were observed during 2005-2015 (5/45), compared to the preceding two decades (20/47 and 15/33; p=0.0016**). A non-significant trend towards greater NTR during 2005-2015 was observed (p=0.1180) (*Table 3*).

During the first, second and third decades 26/37 (70%), 21/25 (84%) and 45/49 (92%) of cases received chemotherapy (χ^2; p=0.439; n=111). We were unable to accurately quantify this variable in 25/136 (18.4%) all occurring during the first two decades. From 1995 to 2005 high-risk patients fit for chemotherapy received VEC. During the most recent decade standard risk cases were treated with VEC, high-risk cases received vincristine, carboplatin, etoposide (JOE) alternating with vincristine, cisplatin, etoposide and cyclophosphamide (OPEC).

Contrasted CT was the imaging modality available during 1985-1995. MRI imaging only became available towards the end of the first decade with full implementation during the middle and last decades. Early post-operative MRI, to determine extent of resection, only became standard practice in 2011 (*Table 3*).

Univariate Cox regression analysis (*Figure 4*) of our data suggest that therapeutic decade 2005-2015 (p=0.0315*), Linac technology (p=0.0216*), standard risk MB (p=0.0017**), age 3-15 years (p=0.0093**), classic histology (p=0.0301*) and GTR (p=0.0375*) were all independently associated with hazard ratios that significantly favour survival. CSF cytology (p=0.8881), sex (p=0.5985) and leptomeningeal spread (p=0.2935) did not significantly influence outcomes.

Discussion

This single-institution experience describes improvements in OS of patients with MB, treated during three therapeutic decades and relates data to advances in multidisciplinary management in South Africa as representative model of a LMIC. OS5 and OS10 for the entire cohort was 60.5% and 54.6% respectively. Survival, without adjusting for risk, was significantly improved in the final decade, with OS5 and OS10 of 76.2% and 73.2% respectively. Our findings are comparable to outcomes achieved in HIC[5,7,12,22]. Of note is the finding that the relative percentage of standard risk cases were significantly more during the final decade, high-risk cases remained unchanged and incompletely staged cases declined. This shift in stratification during the final decade may at least in part underpin a survival benefit. The noted frequency of high-risk cases compared with standard risk cases across

the entire cohort was 71.4%, which is much higher than previous reports from HIC where the ratio is almost reversed[17]. This is most likely a consequence of various factors that include a high number of patients less than three years old, late presentation due to various socio-economic and public health care factors, delays in definitive diagnosis and multimodal management, as well as slow advances in diagnostic and treatment approaches. Similar large proportions of high-risk MB cases have been described in other LMIC including a retrospective synopsis in Morocco where 70% of cases were high-risk[13]. Age-adjusted analysis of our data indicated that 59% of patients aged 3-15 were high-risk, which is in line with other LMIC reports documenting high-risk frequencies of 50-60%[17,23,24]. Overall standard risk MB was significantly less prevalent than the high-risk counterparts and constituted only 28.6% of our cohort with OS5 of 78.7%, comparable to international outcomes of 80-85%. OS5 of high-risk cases was 51.2% which is lower than internationally reported rates of 65-70%[16,17].

We further quantified survival in the context of the respective risk constituents. The finding that young patients exhibited very poor outcomes was not surprising. Historically survival rates for this group have been dismal, seldom exceeding 25-45%[8,25,26] and this is in line with the OS5 of 32.5% we observed. Demographic data indicated that 26.5% of our cohort were children aged less than three years which is higher than reported figures of 10-20%[27,28]. Others have suggested that one third of MB cases occur before the age of three which is more consistent with our findings[29]. The unfavourable outcomes we observed may in part be explained by higher rates of metastatic disease at diagnosis and different underlying biology in young children. Furthermore, the wide-spread reluctance to expose the immature brain to craniospinal radiotherapy and its significant long-term radiotherapy effects, contributes to sub-optimal tumour eradication[29].

Metastatic dissemination is characterised by malignant cells in the CSF and/or leptomeningeal spread on CT/MRI imaging[5,15,26]. Despite the uncertainty surrounding the origin of CSF sampling in this cohort, our results for combined CSF analysis are consistent with results from other centres using day 14 post-operative lumbar puncture and/or intracranial CSF samples, reporting CSF dissemination in 20-40% of cases[28,30,31]. Furthermore, we observed leptomeningeal spread on base-line imaging in 20.0% of cases, similar to previously reported numbers[26,30,32]. Findings from this study are in line with previous reports indicating that the presence of neuraxis dissemination on MRI correlated with survival, whereas CSF outcomes did not[30]. Current standard practice includes cytological evaluation of lumbar CSF obtained 14 days post-operatively in conjunction with leptomeningeal assessment on imaging[11].

In line with previous reports quantifying the proportions of histological variants, our results indicated that classic histology (72.7%) was most prevalent, followed by desmoplastic nodular/MBEN (17.2%)

and LCA (10.1%) histology respectively. This is consistent with other reports indicating that LCA and desmoplastic nodular MBEN occur at frequencies of 10-22% and 7-30% respectively, with classic tumours constituting the remainder[33]. Furthermore, LCA histology was associated with inferior OS compared to classic and desmoplastic variants. The OS of classic, desmoplastic nodular/MBEN and LCA variants were 66.1%, 58.9% and 39.5% respectively, which are all lower than previously reported[13,17,22].

Historically maximal safe resection with GTR, or at least NTR, is considered optimal neurosurgical standard of care. Maintaining an appropriate balance between extent of resection and respect for surrounding organs at risk is critical. This study revealed superior neurosurgical outcomes demonstrated by significantly greater GTR and fewer STR during the third decade of 2005-2015. This may reflect improved surgical techniques over time, or the change in evaluation since in the earlier part of this series, extent of resection was mostly dependent on surgical opinion only, or at best contrasted CT assessment. MRI as an early postoperative evaluation was only a feature of the latter part of the study. Our data indicates that GTR was associated with significantly greater OS compared to STR/biopsies and that the extent of resection does influence survival. Interestingly, Taylor *et al.* recently reported that the prognostic benefit of extent of resection may be related to specific molecular subgroups only and that NTR or even STR might be considered adequate if likelihood of neurological morbidity is high[34]. However, in the absence of molecular testing maximal safe resection remains standard of care.

It is well established that MB exhibits a male predominance, with a male to female ratio of 1.5-1.9[26,35]. The results from this study however indicated a non-significant female predominance with a male to female ratio of 0.91. Although sex is not incorporated in the modified Chang risk classification, it is generally accepted that male outcomes are less favourable[35]. We observed that males had poorer survival outcomes. Our data revealed differences in histological variants between males and females. Classic histology is associated with more favourable outcomes and our female cohort consisted of a significantly greater number of this sub-type compared to males. In contrast the male sub-cohort consisted of significantly greater LCA variants which carry the worst prognostic outcome of all the sub-types. Classic histology is known to commonly harbour the WNT molecular subgroup which is associated with OS in excess of 90%, whereas LCA variants commonly harbour the group 3 molecular variant which is more common in males, is associated with a high chance of disseminated disease at presentation and inferior OS of 40-50%[31,36]. We speculate that these findings may in part explain the poor outcome of males in this study, although molecular sub-group identification was not performed in our cohort.

We acknowledge the potential bias of stage migration as previously described by Will Rogers[37]. This phenomenon may potentially lead to spurious survival statistics. This time-dependent entity may lead to altered staging outcomes and artificial survival increases in both the less and more advanced disease stages. Despite these potential caveats we show in this study that improved survival was a multifactorial process. During the latter phases of this study, diagnostic imaging and pathology was more advanced, a risk-adapted approach was implemented[11], craniospinal irradiation was performed using CT-based planning and 3DCRT, chemotherapy was more commonly administered, neurosurgical outcomes improved and accessibility to advanced post-operative imaging was greater. Interpretation of relatively rare disease entities and associated small data sets, is limited by the inability to perform accurate multivariate analysis. The alternative is univariate analysis which we applied to assess the contribution of the various associated risk factors. Univariate analysis may however increase the likelihood of type 1 statistical errors and does not allow quantification of each statistical variants' relative contribution to a primary endpoint. Furthermore, the RT modality comparison is confounded since greater numbers of standard risk disease, GTR and cases with leptomeningeal spread were observed during the latter decade. Improved outcomes are complex and multifactorial.

In conclusion we have shown that sequential advances in multimodal management of MB have benefited patients in our LMIC centre over the most recent decade despite a prevalence of high-risk disease. Access to improved imaging modalities, advances in surgical techniques, increased number of patients receiving risk-adapted combination chemo- and/or radiotherapy as well as craniospinal irradiation using a linear accelerator with 3D planning, are considered as contributing factors. Improved methods to more accurately collect easily accessible clinical data is essential for research and prospective trials need to be prioritised to address pressing oncological questions. Future work will need to investigate the effect of reduced dose craniospinal irradiation on the occurrence of late side-effects and quality of life in our patients. In addition, the ability to perform molecular studies will need to be addressed since these are providing increasingly powerful evidence for a paradigm shift in the way MBs are approached[38].

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Conflict of Interest Statement

The respective authors report no conflict of interest concerning the research protocols and methods used for this study or the findings outlined in this manuscript.

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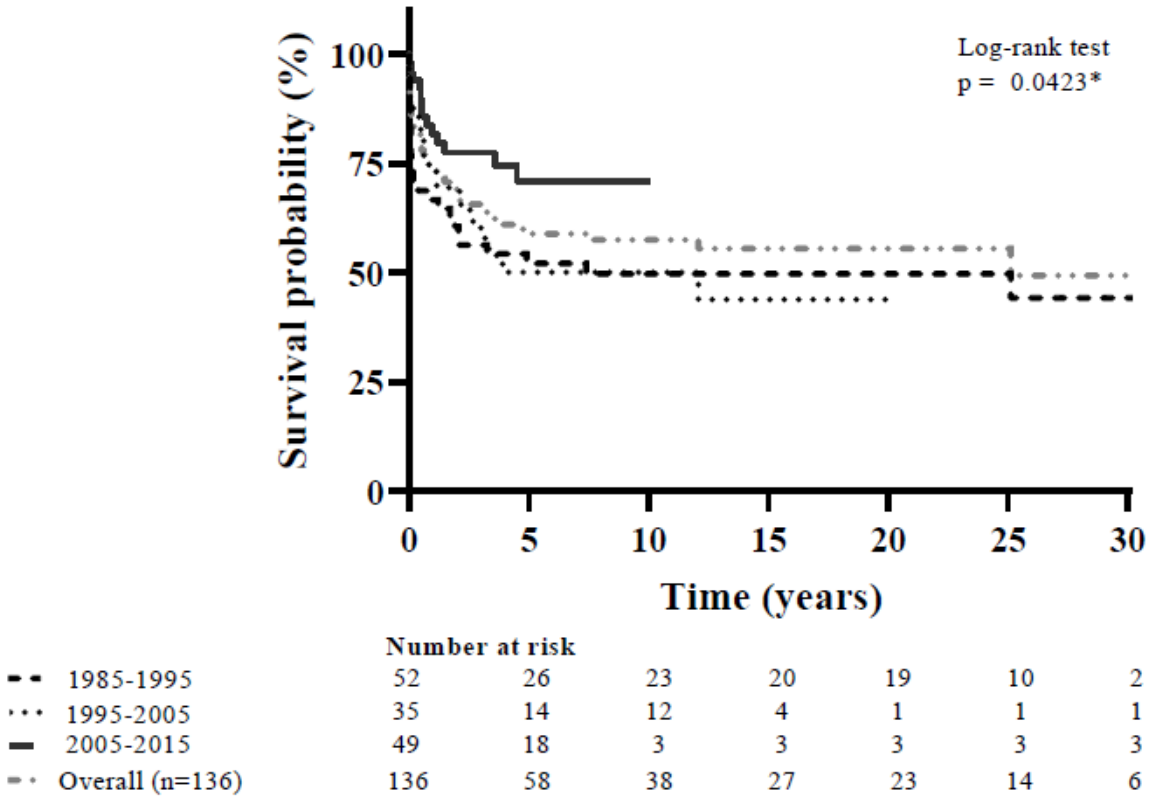
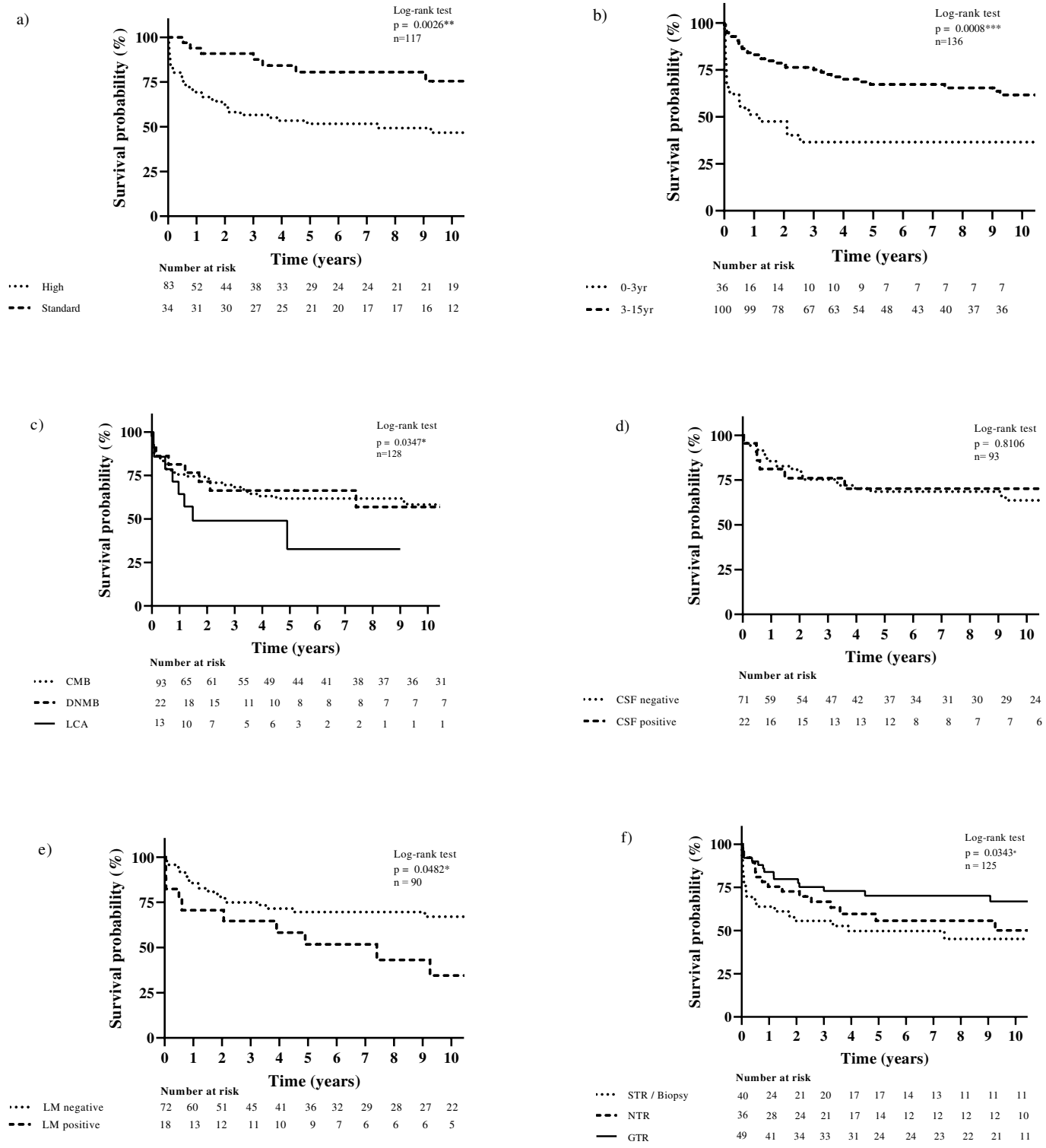


Figure 1: Kaplan-Meyer plots illustrating overall survival during three therapeutic eras for the entire cohort (n=136).



CMB - classic medulloblastoma; DNMB - desmoplastic nodular medulloblastoma; LCA - large cell anaplastic
LM - leptomeningeal; GTR - gross total resection; NTR - near total resection; STR - subtotal resection

Figure 2: Overall survival in context of risk stratification including combined risk (a), age at diagnosis (b), histological subtype (c), cerebrospinal fluid (CSF) results (d), leptomeningeal involvement (e) and extent of resection (f). The evaluable sub-cohort sizes are indicated (n).

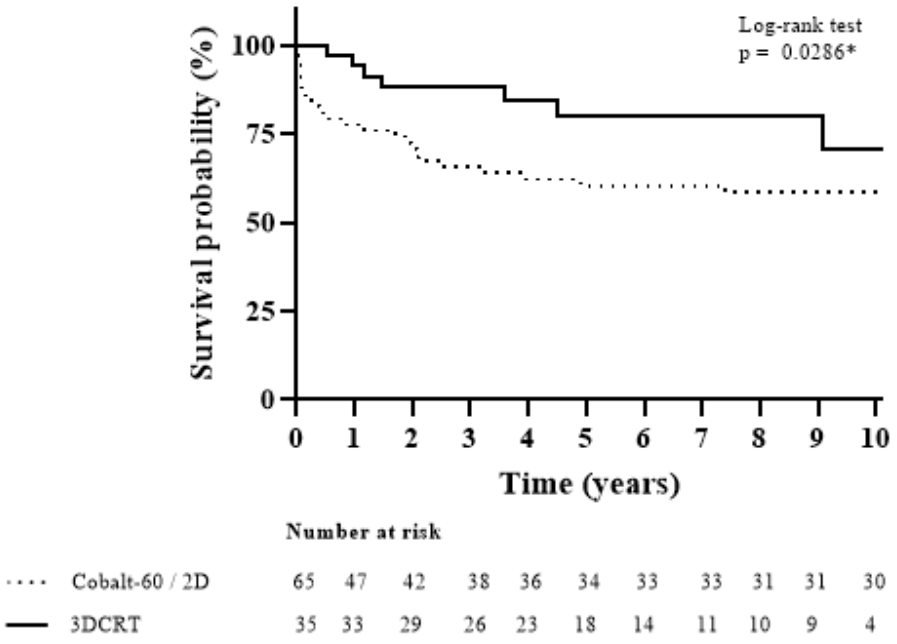
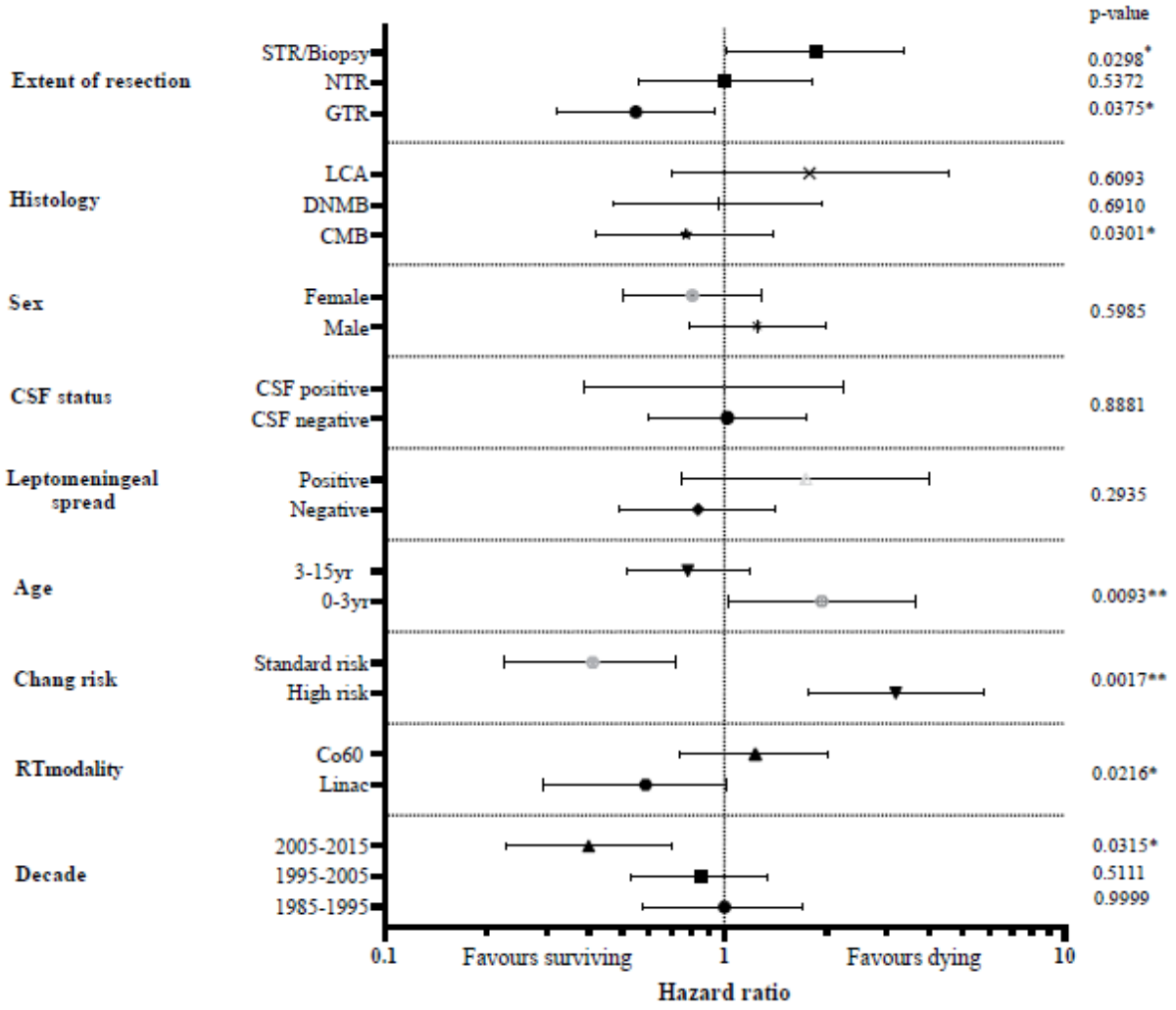
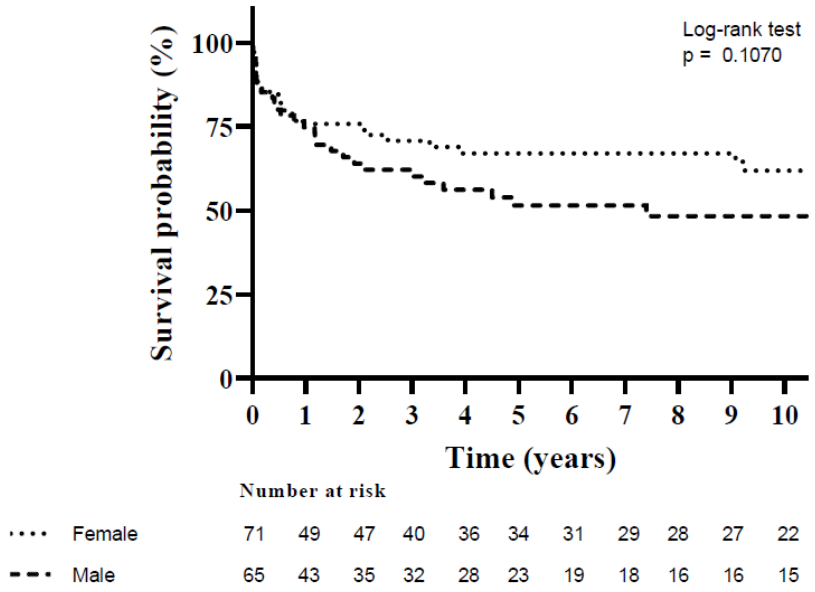


Figure 3: Comparison of evaluable survival outcomes for patients who received 2D radiotherapy on a Cobalt-60 machine (1985-2005), with 3D conformal radiotherapy (3DCRT; 2005-2015) using a linear accelerator (n=100).



CMB - classic medulloblastoma; DNMB - desmoplastic nodular medulloblastoma; LCA - large cell anaplastic; LM - leptomeningeal; GTR - gross total resection; NTR - near total resection; STR - subtotal resection; CSF - cerebrospinal fluid

Figure 4: Forest plot of univariate Cox regression analysis for prediction of mortality. Lines in each row represent 95% confidence intervals and hazard ratios (HR). The central vertical dotted line indicates the HR for null hypothesis. Variable groups decade 1985-1995, DNMB and NTR were designated a reference value with hazard ratio of 1, whereas other sub-groups were normalized to the total evaluable constituent number.



Supplemental Figure A: Ten-year overall survival comparison between female and male patients (n=136).

Supplemental Table A: Comparison of risk factors between female and male patients. The evaluable size of each sub-cohort is indicated (n).

	Female	Male	p-value (Chi-square test)
Number (n=136)	71 (52.2%)	65 (47.8%)	0.3960
Median age at diagnosis (years)	5.5	6.0	-
Number deceased (confirmed)	23/71 (32.4%)	31/65 (47.7%)	0.0807
Histology (n=128)			
Classic	55/67 (82.1%)	38/61 (62.3%)	0.0168*
Desmoplastic	10/67 (14.9%)	12/61 (19.7%)	0.4928
LCA	2/67 (3.0%)	11/61 (18.0%)	0.0068**
Extent of Resection (n=125)			
G*TR*	24/67 (34.3%)	25/58 (41.7%)	0.1562
NTR	23/67 (32.9%)	19/58 (31.7%)	0.3291
STR	18/67 (25.7%)	14/58(23.3%)	0.2985
Biopsy	5/67 (7.1%)	2/58 (3.3%)	0.1973
CSF dissemination (n=93)	10/51 (19.6%)	12/42 (28.6%)	0.3369
Leptomeningeal spread (n=90)	12/50 (24%)	6/40 (15.0%)	0.1923
Chemotherapy received (n=136)	86.9%	80.1%	0.4892
Radiotherapy received (n=100)	77.7%	79.8%	0.3091
High Risk Disease (n=117)	68.3%	73.6%	0.5472

Abbreviations: GTR – gross total resection, NTR – near total resection, STR – subtotal resection, CSF – cerebrospinal fluid, LCA – Large Cell Anaplastic

Table 1: Demographic and clinical characteristics of the medulloblastoma cohort. The evaluable numbers for each constituent are indicated (n).

	Age < 3	**Age 3-15**	**All patients**
Number (n=136)	36/136 (26.5%)	100/136 (73.5%)	136
Incidence (per annum)	1.21	3.31	4.52
Gender ratio (Male:Female)	0.90	0.93	0.91
Median age at diagnosis (years)	2.1	7.3	5.7
Histology (%) n=128			
Classic	68.6% (24/35)	74.2% (69/93)	72.7% (93/128)
Desmoplastic / Nodular	20.0% (7/35)	16.1% (15/93)	17.2% (22/128)
Large Cell Anaplastic	11.4% (4/35)	9.7% (9/93)	10.1% (13/128)
CSF metastases (%) n=93			
Positive	23.8% (5/21)	23.6% (17/72)	23.7% (22/93)
Negative	76.2% (16/21)	74.4% (55/72)	76.3% (71/93)
Leptomeningeal spread (%) n=90			
Positive	19.0% (4/21)	20.3% (14/69)	20.0% (18/90)
Negative	81.0% (17/21)	79.7% (55/69)	80.0% (72/90)
Modified Chang Risk Stratification (%) n=119			
Standard	0% (0/36)	41% (34/83)	28.6% (34/119)
High	100% (36/36)	59.0% (49/83)	71.4% (85/119)

Abbreviations: CSF – cerebrospinal fluid

Table 2: Risk factor distribution between therapeutic eras.

	1985 - 1995	1995 - 2005	2005 – 2015	p-value
Total Number Per Decade n=136	n=52	n=35	n=49	
Chang Risk Stratification				
Standard	7 (13.5%)	7 (20.0%)	20 (40.8%)	0.0048**
High	32 (61.5%)	22 (62.9%)	29 (59.2%)	0.9394
Incomplete	13 (25.0%)	6 (17.1%)	0 (0.00%)	N/A
Age				
0-3y	15 (28.8%)	11 (31.4%)	10 (20.4%)	0.8640
3-15y	37 (71.2%)	24 (68.6%)	39 (79.6%)	0.8911
Histology				
Classic	37 (71.2%)	26 (74.3%)	30 (61.2%)	0.3848
Desmoplastic	10 (19.2%)	5 (14.3%)	7 (14.3%)	0.7486
Large Cell Anaplastic Variant	0 (0.0%)	1 (2.9%)	12 (24.5%)	N/A
Unknown	5 (9.6%)	3 (8.5%)	0 (0.0%)	N/A
Extent of resection				
GTR	16 (30.8%)	10 (28.6%)	23 (46%)	0.0310*
NTR	11 (21.2%)	8 (22.9%)	17 (41%)	0.3507
STR/Biopsy	20 (38.5%)	15 (42.9%)	5 (12%)	0.003**
Unknown	5 (9.5%)	2 (5.7%)	4 (8.2%)	N/A
CSF metastases				
Positive	2 (3.8%)	4 (11.4%)	16 (32.7%)	N/A
Negative	21 (40.4%)	18 (51.4%)	32 (65.3%)	0.6418
Unknown	29 (55.8%)	13 (37.2%)	1 (2.0%)	N/A
Leptomeningeal spread				
Positive	9 (17.3%)	4 (11.4%)	5 (10.2%)	0.5373
Negative	14 (26.9%)	17 (48.6%)	41 (83.7%)	0.001**
Unknown	29 (55.8%)	14 (40.0%)	3 (6.1%)	N/A

Abbreviations: CSF – cerebrospinal fluid
N/A - Not Applicable due to small sample size

Table 3: Constituents of multidisciplinary management (n=136). Outcomes are expressed as percentages to indicate evaluable proportions for each subcohort.

Treatment	**1985-1995**	**1995-2005**	**2005-2015**	
Radiotherapy	n=52	n=35	n=49	
Cobalt-60 (2D)	44	21	-	
Linac 6MV (3D)	-	-	35	
Unknown	8	14	14	
Craniospinal dose	31.5-36.8Gy	33.5-37.0Gy	Standard risk: 23.4Gy High risk: 36Gy	
Boost to tumour bed	21.0Gy	21.0-24.1Gy	Standard risk: 30.6-32.4Gy High risk: 18-19.8Gy	
Fractions per week	4-5	4-5	4-5	
Dose per fraction	1.2-1.7Gy	1.3-1.9Gy	1.8Gy	
Surgery	n=52	n=35	n=49	
GTR	16/47 (31%)	10/33 (30%)	23/45 (51%)	*p=0.0310**
NTR	11/47 (23%)	8/33 (24%)	17/45 (38%)	*p=0.1180*
STR/Biopsy	20/47 (42%)	15/33 (46%)	5/45 (11%)	*p=0.0016***
Unknown	*5 (1%)*	*2 (6%)*	*4 (8%)*	*N/A*
Chemotherapy	n=52	n=35	n=49	
Received	26/37 (70%)	21/25 (84%)	45/49 (92%)	*p=0.4397*
Not received	11/37 (30%)	4/25 (11%)	4/49 (8%)	*p=0.563*
Unknown	*15 (29%)*	*10 (29%)*	*0 (0%)*	*N/A*
Imaging availability				
CT	Yes	Yes	Yes	
MRI	No	Yes	Yes	
Overall Survival				
5-year	51.5%	49.3%	76.2%	*p=0.0160**
10-year	49.5%	49.1%	73.2%	*p=0.0321**

Abbreviations: GTR – gross total resection, NTR – near total resection, STR – subtotal resection, 2D – two-dimensional, 3D – three-dimensional

Figure / Table legends

Table 1: Demographic and clinical characteristics of the medulloblastoma study cohort.

Figure 1: Kaplan-Meier plots illustrating overall survival during three therapeutic eras for the entire cohort (n=136).

Table 2: Risk factor distribution between therapeutic eras.

Figure 2: Overall survival in context of risk stratification including combined risk (a), age at diagnosis (b), histological subtype (c), cerebrospinal fluid (CSF) results (d), leptomeningeal involvement (e) and extent of resection (f). The evaluable sub-cohort sizes are indicated (n).

Table 3: Constituents of multidisciplinary management (n=136).

Figure 3: Comparison of evaluable survival outcomes for those who received 2D radiotherapy on a Cobalt-60 machine (1985-2005) with 3D conformal radiotherapy (3DCRT; 2005-2015) using a linear accelerator (n=100).

Figure 4: Forest plot of univariate analysis for determinants of overall survival. Lines in each row represent 95% confidence intervals and hazard ratios (HR). The central vertical dotted line indicates the HR for null hypothesis.

Supplemental Figure A: Ten-year overall survival comparison between female and male patients (n=136).

Supplemental Table A: Comparison of risk factors between female and male patients. The evaluable size of each sub-cohort is indicated (n).