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

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Background: Medulloblastoma (MB) is the commonest malignant brain tumour of childhood. Accurate clinical data on paediatric MB in the low-and-middle-income countries (LMIC) setting are lacking. Sequential improvements in outcomes seen in high-income countries are yet to be reflected in LMICs.

Aim: The aim of this study was 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. The modified Chang criteria were used for risk stratification. The primary objective of this study 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 (CSI) 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 the therapeutic era, three-dimensional (3D) 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 chemotherapy or radiotherapy, as well as CSI using a linear accelerator with 3D planning, are considered as contributing factors.

Keywords: Paediatric brain tumours; medulloblastoma; radiotherapy; 3D conformal radiotherapy; craniospinal irradiation; chemotherapy; paediatric neurosurgery; leptomeningeal spread; cerebrospinal fluid; paediatric oncology; low-and-middle-income countries; Paediatric Oncology in Developing Countries; overall survival.

Introduction

Brain and central nervous tumours are rare in children 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, which is second only to leukaemia constituting 25% of cases. According to international reports, those with brain

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tumours exhibited the lowest survival rate with a median survival time of 18 months compared with 47 months for leukaemia cases.[1,2]

Medulloblastoma (MB) is the most common malignant paediatric brain tumour, comprising 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 embryonic origin and are believed to have originated from progenitor cell lineages present during early brain development. The following four histological variants exist: classic, desmoplastic or nodular, MB with extensive nodularity (MBEN) and large-cell or anaplastic (LCA) histology. In addition, four molecular subgroups, including wingless (WNT), sonic hedgehog (SHH), Group 3 and Group 4, have been identified.[3,4,5,6,7] 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 (HICs) are MB. Data from low-and-middle-income countries (LMICs) exhibit a substantial variation in incidence rates ranging from 6% to 50%.[10,11,12,13,14] The exact epidemiological, clinicopathological characteristics and survival outcomes of MB within South Africa's markedly heterogeneous population are unknown. The 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 follows: age ≥ 3 years at presentation, < 1.5 cm^2 residual tumour after resection, cerebrospinal fluid (CSF) negative for tumour cells, absence of leptomeningeal spread on computed tomography (CT) or magnetic resonance imaging (MRI) and classic or desmoplastic histology. High-risk disease is defined when any of the following are present: age < 3 years, residual tumour of > 1.5 cm^2 after surgery, CSF positive for tumour cells, leptomeningeal spread on CT/MRI or LCA histology.[15,16] Over the last decade, advances in the multidisciplinary management of patients with MB in HICs have resulted in 5-year overall survival (OS) rates of 80%–85% for standard-risk and 65%–70% for high-risk disease.[16,17] This improvement is not apparent in LMICs and may be attributed to common constraints, such as delayed or inaccurate diagnoses with advanced disease at presentation, high rates of hospital acquired infections following neurosurgical intervention and co-morbid illnesses, such as HIV, TB, parasitic disease and malnutrition. Limited access to radiotherapy (RT) services with significant delays from referral to point of treatment, as well as the ever-expanding limitations within socio-economic support structures, further hampers optimal care.[11,18,19]

In order 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 were diagnosed with MB between years 1985 and 2015. 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 0–15 years, who were treated at Red Cross War Memorial and Groote Schuur Hospital complex between 1985 and 2015, was performed. Information obtained from records of oncology, neurosurgery and RT patient 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 RT schedules. Cerebrospinal fluid obtained were either intraoperative cisternal puncture or day 14 post-operative lumbar puncture samples. Because of 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 are, therefore, included in the data tables. 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 – December 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 the years 1992 and 2001, patients received CT scans at Red Cross War Memorial Hospital and MRI scans at the local Medical Research Council facility. Between the years 2001 and 2009, MRI scans were performed at Groote Schuur Hospital. An MRI scanner was introduced at the Red Cross War Memorial Hospital in 2009. Prior to the year 2012, contrasted CT was used to evaluate for leptomeningeal spread during the initial diagnostic assessment. During the later part of this study, MRI was predominantly used. Over time, an immediate post-operative 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 were further cross-referenced with the South African Children's Cancer Study Group (SACCSG) registry.

Radiotherapy

During the first two decades (1985–2005), two-dimensional (2D) planning in combination with a^{60} Co gamma ray unit was used. From 2005 to 2015, all cases were 3D planned with 6 MV photon energy and treated with a linear accelerator (LINAC). From 2007, standard-risk MB was treated with reduced-dose craniospinal irradiation (CSI) consisting of 23.4 gray (Gy) to the craniospinal axis in 13 fractions together with a tumour bed boost of 30.6 Gy – 32.4 Gy in 17–18 fractions. This is in accordance with the Pediatric Oncology in Developing Countries (PODC) Committee of the International Society of Pediatric Oncology (SIOP) adapted treatment recommendations.[11] High-risk disease was treated with a full-dose CSI of 36 Gy in 20 fractions, with a boost dose of 18.0 Gy – 19.8 Gy in 10–11 fractions to the tumour bed.

Selected cases harbouring a significant, gross residual disease occasionally necessitated an additional boost depending on the dose to surrounding organs at risk.

Extent of resection

Prior to the year 2011, contrast-enhanced CT was used for post-operative imaging (usually the day after surgery) and was subsequently replaced by immediate post-operative MRI (< 48 h post-surgery) imaging during the later 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 post-surgical imaging when available. Near total resection (NTR) was defined as < 1.5 cm^2 residual tumour, whereas sub-total resection (STR) represented an incomplete resection with > 1.5 cm^2 residual tumour.

Chemotherapy

Data captured reflect administration of chemotherapy at any point of the patient's journey. During the early phases of this study, chemotherapy was not routinely prescribed, except for high-risk cases, which is most commonly reported in young children under the age of 3–4 years, in whom the expected long-term sequelae of craniospinal RT necessitated delay of RT and the use of alternative treatment modalities. From 1985 to 1995, all high-risk patients received chemotherapy, either because the 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 the year 2005, all high-risk patients and those with standard risk received reduced-dose CSI together with concurrent and adjuvant chemotherapy. After the year 2015, concurrent weekly vincristine was omitted.

Tissue preparation and immunohistochemistry

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

Statistical analysis

Statistical analysis was performed using the GraphPad Prism software. The Kaplan–Meier methodology was applied to quantify survival outcomes. Log-rank tests were used to determine differences between groups.[21] Overall survival was calculated as the 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. In order 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 that are graphically depicted on a Forest plot.

Ethical considerations

Ethics approval was obtained from the Human Research Ethics Committee, University of Cape Town (Reference 777/2018 linked to sub-study 149/2014). Approval renewed 28.8.2020.

Results

Study population and demographics

About 136 patients who had undergone multidisciplinary management for MB between 1985 and 2015 were identified. Demographic and clinical characteristics of the MB cohort are summarised in Table 1. The male-to-female ratio was 0.9, and the median ages at diagnosis were 2.1 and 7.3 years 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 cases, 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 or nodular or MBEN and 13/128 (10.1%) LCA variants. The results of CSF analysed revealed that 22/93 (23.7%) cases were positive for malignant cells. Because of 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 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 or drop metastases in 18 out of 90 (20.0%) evaluable cases.

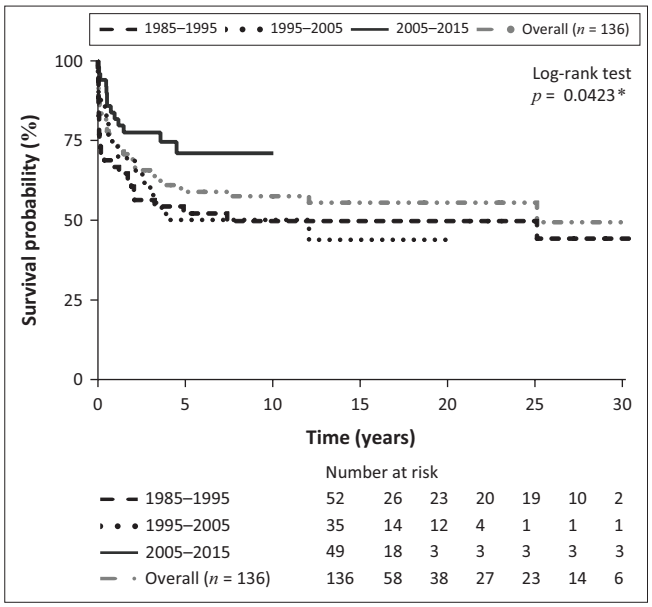
Survival analysis

The 5-year and 10-year OS rates for the entire cohort was 60.5% and 54.6%, respectively (Figure 1). Survival was improved for the most recent decade 2005–2015, in comparison with the preceding two decades (Log-rank test $p = 0.0423$; $n = 136$). The 5-year OS (OS5) rates for the first,

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

Variable	Age < 3		Age 3-15		All patients	
	n	%	*n*	%	*n*	%
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	24/35	68.6	69/93	74.2	93/198	72.7
Desmoplastic / Nodular	7/35	20.0	15/93	16.1	22/128	17.2
Large Cell Anaplastic	4/35	11.4	9/93	9.7	13/128	10.1
CSF metastases (%) *n* = 93						
Positive	5/21	23.8	17/72	23.6	22/93	23.7
Negative	16/21	76.2	55/72	74.4	71/93	76.3
Leptomeningeal spread (%) *n* = 90						
Positive	4/21	19.0	14/69	20.3	18/90	20.0
Negative	17/21	81.0	55/69	79.7	72/90	80.0
Modified Chang Risk Stratification (%) *n* = 119						
Standard	0/36	0.0	34/83	41.0	34/119	28.6
High	36/36	100.0	49/83	59.0	85/119	71.4

CSF, cerebrospinal fluid.



*, equal or less that 0.05.

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

second and third decades were 51.5% (95% confidence interval [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) rates for the first, second and third decades were 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. The OS5 rate during the decade 2005–2015 was significantly higher compared with the decades 1985–1995 ($p = 0.0186$) and 1995–2005 ($p = 0.0319$) when individually compared. No significant difference in OS was observed for periods 1985–1995 versus 1995–2005 ($p = 0.5650$).

An unequal risk distribution amongst therapeutic groups can influence survival assessment and interpretation. Table 2 summarises the prevalence of measurable variables within each group. The decade 2005–2015 was characterised by a significantly greater number of cases with the absence of 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 with high-risk disease (Figure 2a). The OS5 and OS10 rates of standard-risk patients were 78.7% (95% CI 64.7–89.7) and 70.4% (95% CI 60.5–88.6), respectively, compared with 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 constituted 19/136 (13.9%).

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

TABLE 2: Risk factor distribution between therapeutic eras.

Total number per decade *n* = 136	1985–1995 *n* = 52		1995–2005 *n* = 35		2005–2015 *n* = 49		*p*-value
	n	%	*n*	%	*n*	%	
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 (years)							
0-3	15	28.8	11	31.4	10	20.4	0.8640
3-15	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	0.0310*
NTR	11	21.2	8	22.9	17	41.0	0.3507
STR/Biopsy	20	38.5	15	42.9	5	12.0	0.003**
Unknown	5	9.5	2	5.7	4	8.2	N/A
CSF metastases							
Positive	2	3.8	4	11.4	16	32.71	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	NA

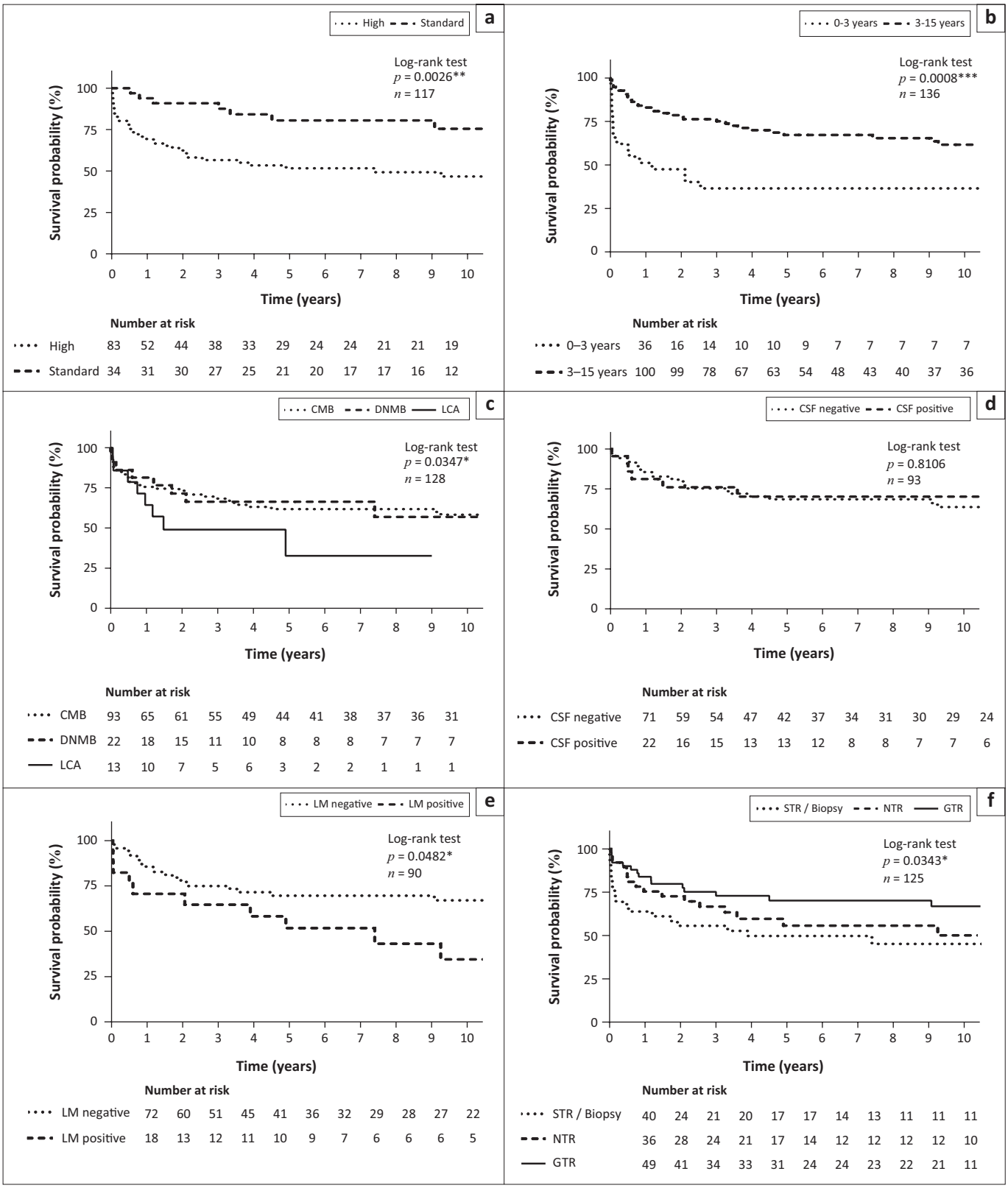
CSF, cerebrospinal fluid; N/A, not applicable due to small sample size; GTR, Gross total resection; NTR, Near Total Resection; STR, sub-total resection.

*, equal or less than 0.05; **, equal or less than 0.01; ***, equal or less than 0.001.

LCA histology was associated with significantly inferior OS compared with classic and desmoplastic variants ($p = 0.0347$; $n = 128$; Figure 2c). Both OS5 and OS10 rates were 39.5% (95% CI 20.8–54.9) for cases with LCA histology. In comparison, classic histology exhibited OS5 and OS10 rates 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 rates of 58.9% (95% CI 38.5–77.1) and 52.8% (95% CI 30.3–70.6; $p = 0.298$).

No significant differences in OS were 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 preoperative diagnostic imaging was associated with reduced survival (Figure 2e). The OS5 and OS10 rates in the absence of leptomeningeal spread were 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 rates 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%) cases for leptomeningeal involvement.

Maximal safe surgical resection was performed by specialised paediatric neurosurgeons throughout the study period. The OS5 and OS10 rates for GTR cases were 69.6% and 66.5%, respectively, compared with 55.5% and 49.4% for NTR cases ($p = 0.2810$). The OS5 and OS10 rates for STR cases were 48.4% and 43.8%, respectively, and were



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.

*, equal or less than 0.05; **, equal or less than 0.01; ***, equal or less than 0.001.

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*).

significantly lower than those for 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 male and female patients; however, a trend towards increased survival was observed for female patients (Supplemental Figure A).

The OS5 and OS10 rates of female patients were 66.8% (95% CI 61.1–72.3) and 61.6% (95% CI 54.7%–67.9%), respectively, compared with male patients with OS5 and OS10 rates of 51.7% (95% CI 44.1–59.2) and 48.4% (95% CI 40.7–55.1; p = 0.1070; n = 136), respectively. 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 patients compared with 38/61 (62.3%) male counterparts (p = 0.0168; n = 128). Only 2/67 (3%) female patients 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 were observed.

Because of the study duration and resultant missing patient data, we could only with certainty evaluate RT outcomes in 100/136 (73.5%) 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 decade of 2005–2015, was associated with OS5 and OS10 rates of 76.2% and 73.2%, respectively. The combined OS5 and OS10 rates 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) cases. The number of GTR achieved during the decade 2005–2015 was 23/45 (51%), which is significantly higher compared with 16/47 (34%) and 10/33 (30%) during the decades 1985–1995 and 1995–2005, respectively (p = 0.0310). There were significantly fewer STRs observed during the decade 2005–2015 (5/45), compared with the preceding two decades (20/47 and 15/33; p = 0.0016). A non-significant trend towards greater NTR was observed during the period 2005–2015 (p = 0.1180; Table 3).

During the first, second and third decades, 26/37 (70%), 21/25 (84%) and 45/49 (92%) cases received chemotherapy (χ^2; p = 0.439; n = 111). We were unable to accurately quantify this variable in 25/136 (18.4%) cases, 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, and high-risk cases received vincristine, carboplatin, etoposide alternating with vincristine, cisplatin, etoposide and cyclophosphamide.

Contrasted CT was the imaging modality available during the decade 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 the extent of resection only became a 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

TABLE 3: Constituents of multidisciplinary management (N = 136)

Treatment	1985–1995	1995–2005	2005–2015	p-value
Radiotherapy (*N*)	**52**	**35**	**49**	**-**
Cobalt-60 (2D)	44	21	-	-
Linac 6MV (3D)	-	-	35	-
Unknown	8	14	14	-
Craniospinal dose	31.5 Gy - 36.8 GY	33.5 Gy - 37.0 Gy	-	-
Standard risk	-	-	23.4 Gy	-
High risk	-	-	36.0 Gy	-
Boost to tumour bed	21.0 Gy	21.0 GY - 24.1 Gy	-	-
Standard risk	-	-	30.6 Gy - 32.4 Gy	-
High risk	-	-	18.0 Gy - 19.8 Gy	-
Fractions per week	4-5	4-5	4-5	-
Dose per fraction	1.2 Gy - 1.7 Gy	1.3 Gy - 1.9 Gy	1.8 Gy	-
Surgery (*N*)	**52**	**35**	**49**	**-**
GTR	-	-	-	0.0310*
GTR: 1985–1995 (n = 47)	16	-	-	-
GTR: 1985–1995 (%)	31	-	-	-
GTR: 1995–2005 (n = 33)	-	10	-	-
GTR: 1995–2005 (%)	-	30	-	-
GTR: 2005–2015 (n = 45)	-	-	23	
GTR: 2005–2015 (%)	-	-	51	
NTR:				0.118
NTR: 1985–1995 (n = 47)	11	-	-	-
NTR: 1985–1995 (%)	23	-	-	-
NTR: 1995–2005 (n = 33)	-	8	-	-
NTR: 1995–2005 (%)	-	24	-	-
NTR: 2005–2015 (n = 45)	-	-	17	-
NTR: 2005–2015 (%)	-	-	38	-
STR/Biopsy (N)	-	-	-	0.0016**
STR/Biopsy: 1985–1995 (n = 47)	20	-	-	-
STR/Biopsy: 1985–1995 (%)	42	-	-	-
STR/Biopsy: 1995–2005 (n = 33)	-	15	-	-
STR/Biopsy: 1995–2005 (%)	-	46	-	-
STR/Biopsy: 2005–2015 (n = 45)	-	-	5	-
STR/Biopsy: 2005–2015 (%)	-	-	11	-
Unknown	-	-	-	N/A
Unknown: 1985–1995 (n)	5	-	-	-
Unknown: 1985–1995 (%)	1	-	-	-
Unknown: 1995–2005 (n)	-	2	-	-
Unknown: 1995–2005 (%)	-	6	-	-
Unknown: 2005–2015 (n)	-	-	4	-
Unknown: 2005–2015 (%)	-	-	8	-
Chemotherapy (*N*)	52	35	49	-
Received	-	-	-	0.4397
Received: 1985–1995 (n = 37)	26	-	-	-
Received: 1985–1995 (%)	70	-	-	-
Received: 1995–2005 (n = 25)	-	21	-	-
Received: 1995–2005 (%)	-	84	-	-
Received: 2005–2015 (n = 49)	-	-	45	-
Received: 2005–2015 (%)	-	-	92	-
Not received	-	-	-	0.563
Not received: 1985–1995 (n = 37)	11	-	-	-
Not received: 1985–1995 (%)	30	-	-	-
Not received: 1995–2005 (n = 25)	-	4	-	-
Not received: 1995–2005 (%)	-	11	-	-
Not received: 2005–2015 (n = 49)	-	-	4	
Not received: 2005–2015 (%)	-	-	8	
Unknown	-	-	-	N/A
Unknown: 1985–1995 (n)	15	-	-	-

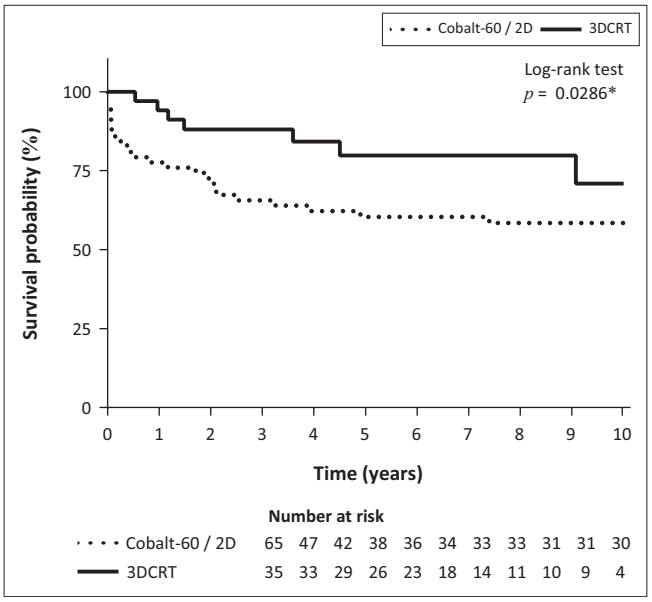
Table 3 continues on the next page →

TABLE 3 (continues): Constituents of multidisciplinary management (N = 136).

Treatment	1985–1995	1995–2005	2005–2015	*p*-value
Unknown: 1985–1995 (%)	29	-	-	-
Unknown: 1995–2005 (*n*)	-	10	-	-
Unknown: 1995–2005 (%)	-	29	-	-
Unknown: 2005–2015 (*n*)	-	-	0	-
Unknown: 2005–2015 (%)	-	-	0	-
Imagine availability	-	-	-	-
CT	Yes	Yes	Yes	-
MRI	No	Yes	Yes	-
Overall survival	-	-	-	-
5-year	-	-	-	0.0160*
%	51.5	49.3	76.2	-
10-year	-	-	-	0.0321*
%	49.5	49.1	73.2	-

GTR, gross total resection; NTR, near total resection; STR, subtotal resection; 2D, two-dimensional; 3D, three-dimensional; CT, computerized tomography; MRI, magnetic resonance imaging.

*, equal or less than 0.05; **, equal or less than 0.01; ***, equal or less than 0.001.



3DCRT, 3D (three-dimnsional) conformal radiotherapy; 2D, two-dimensional.

*, equal or less than 0.05.

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).

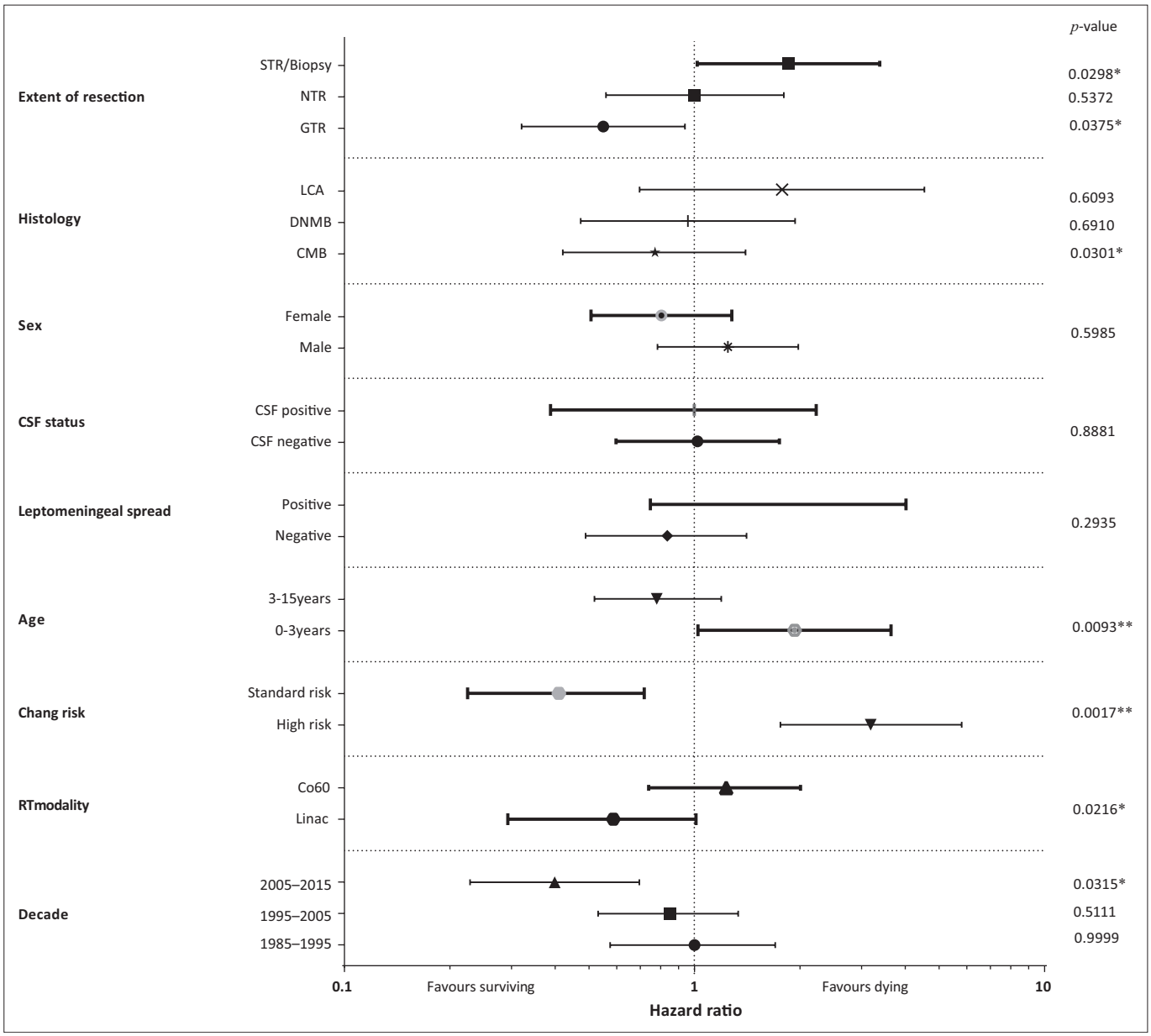
technology (p = 0.0216), standard-risk MB (p = 0.0017), age 3–15 years (p = 0.0093), classic histology (p = 0.0301) and GTR (p = 0.0375) were all independently associated with hazard ratios that significantly favoured survival. CSF cytology (p = 0.8881), sex (p = 0.5985) and leptomeningeal spread (p = 0.2935) did not significantly influence outcomes.

Discussion

This single-institution experience describes improvements in the OS of patients with MB, who are treated during the three therapeutic decades, and relates data to advances in the multidisciplinary management of MB in South Africa as representative model of a LMIC. The OS5 and OS10 rates for the entire cohort were 60.5% and 54.6%, respectively. Survival, without adjusting for risk, was significantly improved in the final decade, with OS5 and OS10 rates of 76.2% and 73.2%, respectively. The findings of this study are comparable with outcomes achieved in HICs.[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 HICs where the ratio is almost reversed.[17] This is most likely the result of various factors that include a large number of patients less than three years old, late presentation because of various socio-economic and public healthcare factors, delays in definitive diagnosis and multimodal management, and slow advances in diagnostic and treatment approaches. Similar large proportions of high-risk MB cases have been described in other LMICs, 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 under the age group 3–15 years were of 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 a OS5 rate of 78.7%, comparable with international outcomes of 80% – 85%. The OS5 rate of high-risk cases was 51.2%, which is lower than the 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 rate of 32.5% we observed. Demographic data suggested that 26.5% of our cohort were children aged less than three years, which is higher than the 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 the findings of this study.[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 widespread reluctance to expose the immature brain to craniospinal RT and its significant long-term RT effects contribute to removal of sub-optimal tumour.[29]

Metastatic dissemination is characterised by malignant cells in the CSF or leptomeningeal spread on CT or MRI imaging.[5,15,26] Despite the uncertainty surrounding the origin of CSF sampling in this cohort, the results of this study for combined CSF analysis are consistent with those 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 baseline imaging in 20.0% of cases, similar to previously reported numbers.[26,30,32] The findings of this study are in line with previous reports, indicating that the presence of neuraxis dissemination on



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.

*, equal or less than 0.05; **, equal or less than 0.01.

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.

MRI correlated with survival, whereas CSF outcomes did not.[30] The 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, the results of this study revealed that classic histology (72.7%) was most prevalent, followed by desmoplastic nodular or MBEN (17.2%) and LCA (10.1%) histology. This is consistent with other reports, indicating that LCA and desmoplastic nodular or 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 with classic and desmoplastic variants. The OS rates of classic, desmoplastic nodular or MBEN and LCA variants were 66.1%, 58.9% and 39.5%, respectively, which are all lower than the previously reported rates.[13,17,22]

Historically, maximal safe resection with GTR, or at least NTR, is considered to be optimal neurosurgical standard of care. Maintaining an appropriate balance between the 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, the extent of resection was mostly dependent on the surgical opinion only, or at best contrasted CT assessment. MRI as an early post-

operative evaluation was only a feature of the later part of the study. The data of this study indicate that GTR was associated with significantly greater OS compared with STR or biopsies, and that the extent of resection does influence survival. Interestingly, Taylor et al. recently reported that the prognostic benefit of the extent of resection may be related to specific molecular subgroups only, and that NTR or even STR might be considered adequate if the likelihood of neurological morbidity is high.[9] However, in the absence of molecular testing, maximal safe resection remains the standard of care.

It is well established that MB exhibits a male predominance, with a male-to-female ratio of 1.5–1.9.[26,34] The results of this study, however, revealed a non-significant female predominance with a male-to-female ratio of 0.91. Although sex is not incorporated into the modified Chang risk classification, it is generally accepted that male outcomes are less favourable.[34] We observed that male patients had poorer survival outcomes. The data of this study revealed differences in histological variants between male and female patients. Classic histology is associated with more favourable outcomes, and the female cohort of this study consisted of a significantly greater number of this sub-type compared with the male cohort. 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 greater than 90%, whereas LCA variants commonly harbour the group-3 molecular variant more common in males, which is associated with a high chance of disseminated disease at presentation with an inferior OS of 40%–50%.[31,35] We speculate that these findings may in part explain the poor outcome of male patients 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.[36] 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. In this study, despite these potential caveats, we show that improved survival was a multifactorial process. During the later phases of this study, diagnostic imaging and pathology were more advanced, a risk-adapted approach was implemented,[11] CSI 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 variant's relative contribution to a primary endpoint. Furthermore, the RT modality comparison is confounded as greater numbers of standard-risk diseases, GTR and cases with leptomeningeal spread were observed during the later decade. Improved outcomes are complex and multifactorial.

Conclusion

We have shown that sequential advances in the multimodal management of MB have benefitted patients in our LMIC setting 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 chemotherapy or radiotherapy, as well as CSI using a linear accelerator with 3D planning, are considered as contributing factors. Improved methods to more accurately collect easily accessible clinical data are essential for research, and prospective trials need to be prioritised to address pressing oncological questions. Future work should investigate the effect of reduced-dose CSI on the occurrence of late side-effects and quality of life in the patients of this study. In addition, the ability to perform molecular studies will need to be addressed, as these are providing increasingly powerful evidence for a paradigm shift in the way MBs are approached.[37]

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Competing interests

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

Authors' contributions

The following authors contributed to this study: J.R. conducted literature review, data acquisition and statistical analysis, writing, review and editing of the article. A.F. provided neurosurgical support and access or assistance with surgical data. A.F. also assist with the article paper review and edits. A.D. provided paediatric oncology support, guidance, and data. A.D. also performed review and edits of the article. C.S. assisted with data acquisition, analysis, evaluation of first draft, radiation oncology guidance and support. K.P. provided pathology support and evaluation of immunohistochemical outcomes. T.K. provided radiology

support or expertise, historical feedback, data review and paper assessment. J.P. was the primary supervisor and paediatric radiation oncology support/guidance. J.P. also assisted with Project initiation, access to data or resources, statistical guidance, article reviews and edits.

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Data availability

No restrictions on data availability. No unique identifiers. Raw data available as Excel spreadsheet on request from the corresponding author.

Disclaimer

The views and opinions expressed in this research article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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Appendix 1

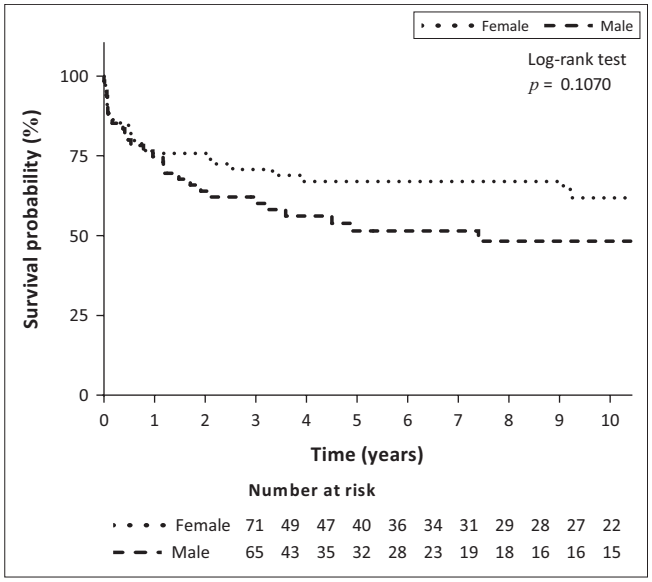

FIGURE 1-A1: Ten-year overall survival comparison between female and male patients (*n* = 136).

TABLE 1-A1: Comparison of risk factors between female and male patients. The evaluable size of each sub-cohort is indicated (*n*).

Variable	Female		Male		*p*-value (Chi-square test)
	n	%	*n*	%	
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)					
GTR	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

GTR, gross total resection; NTR, near total resection; STR, subtotal resection; CSF, cerebrospinal fluid; LCA, large cell anaplastic.

*, equal or less than 0.05; **, equal or less than 0.01.