Barriers and Clinical Factors Influencing Outcomes of Older Children with Medulloblastoma in a Resource Limited Setting - Peru

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Abstract

Background: Medulloblastoma is the most common malignant brain tumor in children. We aim to determine the survival in children with medulloblastoma at the Instituto Nacional de Enfermedades Neoplasicas (INEN) between 1997 to 2013 in Peru, a low-middle income country at the time of this analysis. We also describe the barriers and factors influencing outcomes. Methods: Between 1997-2013, data from 103 children older than 3 years with medulloblastoma were analyzed. Two groups of treatment were identified 1997 – 2008 and 2009 – 2013. Event-free (EFS) and overall survival (OS) were obtained using Kaplan-Meier method and prognostic factors by univariate analysis (log-rank test). A survey was created to identify factors that may have influenced outcome. Results: Eighty-nine patients were included; median age was 8.1 years (range: 2.9-13.9 years). Surgical resection was complete in 39 patients. The five-year OS was 63% (95% CI: 53 – 74%) while EFS was 59% (95% CI: 49 – 71%). The variables adversely affecting survival were: anaplastic histology [compared to desmoplastic; OS: HR=3.5, p=0.03; EFS: HR=3.4, p=0.03], metastasis [OS: HR=3.4, p=0.01; EFS: HR=4.4, p=0.003], and treatment post-2008 [OS: HR=2.5, p=0.01; EFS: HR=2.5; p=0.01]. Conclusions: Outcomes for Medulloblastoma at INEN are low compared with high-income countries (HIC). Univariate analysis demonstrated that histological sub-type, metastasis at diagnosis, and treatment post-2008 all negatively affected outcomes in our study. The importance of multidisciplinary teamwork in the care of children with pediatric brain tumors as well as partnerships with loco-regional groups and colleagues in HIC is vastly beneficial.

Introduction

The burden of pediatric cancer worldwide is estimated to be at nearly 160,000 new cases each year [1, 2]. Advances in the understanding of the molecular and cellular biology of pediatric malignancies, as well as advances in diagnosis, treatment, and supportive care have increased the total cure rate for children in high-income countries (HIC) to 80% [3]. However, 80% of children with cancer worldwide live in low-to middle-income countries (LMIC) and do not have access to the same level of care, leading to inferior outcomes [1, 2].

As the rates of communicable diseases and other causes of early childhood mortality have decreased in LMIC due to improving healthcare infrastructure, it is imperative to undertake the mission of providing today's

advances in cancer care to all children worldwide. Several consortia formed between institutions in North America and Europe and institutions in LMIC have demonstrated the positive impact that global cooperative efforts can have on improving outcomes for pediatric cancer patients in LMIC [1, 4]. Acute lymphoblastic leukemia is one such example where international efforts have improved outcomes[5]. In Recife, Brazil, creating standardized regimens for treatment and supportive care increased the 5-year event free survival (EFS) from 32% to 63% over a 20-year period[6]. While outcomes have begun to improve for hematologic malignancies in LMIC, survival for patients with solid tumors such as PBT have relatively poor outcomes in LMIC compared to HIC[7-10]. Given the discrepancy in survival rates for children with brain tumors in LMIC compared to HIC, it is important to study the factors affecting those outcomes in LMIC so that interventions can be made to improve survival.

Medulloblastoma is the most common malignant brain tumor of childhood and is an embryonal tumor of the posterior fossa that arises from transformed progenitor cells within the developing cerebellum[11, 12]. It can arise at any age with the most frequent age at presentation being between 5-9 years [13]. The current management of medulloblastoma for children greater than three years of age involves maximum resection of the primary tumor followed by risk-adapted craniospinal radiation (CSI) with boost to tumor bed (total radiation dose of 54-60Gy) and maintenance chemotherapy[13, 14]. Radiation (CSI dose 23.4Gy) plus adjuvant chemotherapy can be used in standard-risk patients with excellent outcomes and radiation (with CSI dose of 36Gy) plus adjuvant chemotherapy improves survival in high-risk patients[15-17]. While the next generation of clinical trials are using molecular data to classify and risk stratify patients based on seminal work by Michael Taylor and colleagues, for the last several decades, risk stratification in patients over three years of age with medulloblastoma has relied primarily on two clinical variables, extent of residual tumor after surgery and presence of metastatic disease at diagnosis as graded by Chang criteria. Patients considered to be high-risk have residual tumor area greater than 1.5cm2 and/or evidence of dissemination in cerebrospinal fluid, leptomeninges, or extracranial sites at time of diagnosis [18-20].

In order to help improve outcomes for children with medulloblastoma in LMIC, we must first gain an understanding of the current resources, barriers, and outcomes. Therefore, we performed a retrospective analysis of the clinical, histological, and survival characteristics of children greater than three years of age diagnosed with medulloblastoma and treated at The National Institute for Neoplastic Disease (INEN) the largest National referral center, treating 65% of all Pediatric Cancer in Peru. Our primary objectives were to: 1) describe the demographics, clinical characteristics, and management of children with medulloblastoma in Peru, 2) quantify survival outcomes of children with medulloblastoma in Peru, and 3) compare survival outcomes between groups to identify factors that may affect outcomes in Peru.

Methods

Patient population:

Patients from 3 to 15 years old and with the histological diagnosis of Medulloblastoma from the National Cancer Institute in Peru (INEN, "Instituto Nacional de Enfermedades Neoplásicas") were analyzed retrospectively between 1997 to 2013, the patients were categorized into two time periods based on timing of diagnosis, 1997-2008 and 2009-2013, due to the different treatment approach. Histopathological diagnosis of medulloblastoma was confirmed by pathology review by one expert neuropathologist (S.C.). Survival status was obtained from de-identified registry data. This study was approved by the institutional review board at the INEN. Complete clinical records were available for 89 cases from a total of 103 patients identified having medulloblastoma. Collected de-identified data included patient demographic and clinical characteristics such as: age, sex, demographical information, time between symptom onset and initiation of treatment, pathological diagnosis, incidence of ventriculoperitoneal drain placement, post-operative residual as assessed by MRI, availability of cerebrospinal fluid (CSF) analysis, and outcome.

To gain a comprehensive understanding of resources and barriers at INEN, we created a survey to be completed by treating physicians (oncologist, pathologist, neurosurgeon and radiologist at the INEN) to evaluate the resources available at the institution providing pediatric neuro-oncology services between 1997-

2008 and 2008-2013. This survey was approved by the institutional review board at Nationwide Children's Hospital.

Initial Staging and Therapy:

Staging data was categorized into two time periods, 1997-2008 and 2009-2013.

Period 1997 – 2008

No evaluation for metastasis by pre-operative spinal MRI or CSF collection was done in this period [20]. Maximum safe surgical resection was attempted. Post-operative brain and spine MRIs were not routinely obtained. All patients received CSI at a dose of 36Gy with an additional boost to the posterior fossa of 18-24Gy for a total dose of 54-60Gy given in fractions of 1.8Gy five times per week. Patients received maintenance chemotherapy consisting of eight, 21-day cycles of 1.5mg/m2 vincristine on day 1, oral 40mg/m2 prednisone, and 100mg/m2 procarbazine on days 1-10.

Period 2008 - 2013

The extent of disease was assessed by the Chang classification. Maximum safe surgical resection was attempted. Post-operative brain and spine MRIs were obtained within a month after surgery. CSF analyses were performed prior to initial treatment. Patients were classified as high risk based on the presence anaplastic subtype, evidence of metastasis, and/or residual tumor >1.5cm2. All patients received CSI at a dose of 36Gy with an additional boost to the posterior fossa of 18-24Gy for a total dose of 54-60Gy given in fractions of 1.8Gy five times per week.

Patients received weekly 1.5mg/m2 vincristine concomitantly with radiation. Patients then received maintenance chemotherapy consisting of eight cycles of vincristine, cisplatin, and cyclophosphamide. Vincristine was given on days 1, 8, 15 at a dose of 1.5mg/m2. Cisplatin was given on day 1 at a dose of 75mg/m2. Finally, cyclophosphamide was given on days 22 and 23 at a dose of 1000mg/m2 [17].

Statistical analysis

All data were summarized using standard descriptive statistics. Event-free (EFS) and overall survival (OS) estimates were obtained using the Kaplan-Meier method and presented with corresponding 95% confidence intervals. EFS was defined as the time elapsed from diagnosis to the date of first progression, death, or censoring. OS was defined as the time elapsed from diagnosis to death or censoring. Cox proportional hazard models were used to assess the effect of demographic and clinical variables on survival. Model estimates were presented as hazard ratios and corresponding 95% confidence intervals. All p-values were two-sided and those <0.05 were considered statistically significant. Statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria) with the survival and survminer packages.

Results

Treating institution and available pediatric neuro-oncology resources

Results from the administered survey are available **Table 1** . We queried the hospital registry for new cancer diagnoses during our study periods. The INEN had 450-500 new pediatric solid and hematological cancer diagnoses per year, of which, 40-45 were CNS tumors. Between 1997-2007, there were four general pediatric oncologists who provided care to all patients with hematological and solid tumors. The total number of pediatric oncologists increased to eight during the second period at INEN. There were three neurosurgeons at INEN prior to 2008 and five general neurosurgeons during the second time period, however, none had pediatric subspecialty training. Brain and spine MRIs were not routinely obtained prior to surgery nor within 48 hours of surgery. During the first time period there was no MR imaging available at INEN, thus, MR imaging was obtained at private imaging centers, though availability, insurance issues, and the prohibitive out of pocket costs delayed imaging 2-3 months after surgery. The INEN acquired on-site MR imaging in 2008, after which, the delay in obtaining post-operative MRI in the second period decreased to approximately one month. There were ten radiologists on staff prior to 2008 which increased to fifteen radiologists after

2008. Three radiologists concentrated on CNS tumor imaging. There were ten pathologists at the INEN prior to 2008 with one trained in neuropathology, the number of both increased to 12 and two respectively after 2008. The availability of antibodies for immunohistochemistry are describe in **Supplemental Table 1** . Lastly, there were one radiation oncologists dedicated to neuro-oncologic radiation therapy for children and adults. Radiation therapy was delivered via photon radiation therapy throughout these study periods, intensity-modulated radiation therapy was introduced in 2014.

Patient demographics and baseline characteristics

Patient characteristics are detailed in **Table 2** and**Figure 1** demonstrates place of birth of the patients. Between January 1997 and December 2013, there were 89 patients diagnosed with medulloblastoma that were included in this study with nearly half of the patients originated from Lima (n=43, 48%, Figure 1). The median age was 8.1 years (range: 2.9-13.9 years) with a male: female ratio was 1.62:1. The most common presenting symptoms at presentation were headache (96%), ataxia (88%), and nausea/vomiting (87%). Details regarding histology were available in 45/89 patients. Of these 45 patients, histologic subtypes included classic medulloblastoma (n= 21, 47%), desmoplastic/extensive nodularity (n=13, 29%), and large cell/anaplastic subtypes (n=11, 24%). Cases of unclassified medulloblastoma occurred almost entirely prior to 2008. Due to an increased availability of MRI and/or CSF examination for patients who were treated post-2008 (n=38) there are additional details on risk stratification and metastatic stage. While 20 (52%) of post-2008 patients presented without evidence of metastatic disease, the majority of non-metastatic patients were defined as high-risk due to presence of large residual tumor (n=12, 60%).

Clinical Management.

Clinical management of patients are detailed on **Table 3** . All patients received maximal surgical resection following diagnosis. Residual tumor area was only obtained in post-2008 patients and was greater than 1.5 cm2 in 19 patients (50%). Radiation occurred within 50 days of surgery in 53 patients (60%). Seventy-five patients (84%) received chemotherapy within 60 days of completing radiation. Classic was the most common histological subtype (24%), though a substantial portion of patients were diagnosed with unclassified medulloblastoma (49%). Metastasis at diagnosis was documented in 7 out of 38 (18%) patients in the post-2008 cohort.

Survival Outcomes

The five-year OS throughout the time-period of 1997-2013 was 63% (95% CI: 53 – 74%) while EFS at five years was observed to be 59% (95% CI: 49 – 71%) (**Figure 2A**). The 5-year OS and EFS estimates for those diagnosed post-2008 were observed to be 47% (95% CI: 33 – 68%) and 42% (28 – 62%), and the 5-year OS and EFS for those diagnosed pre-2008 were 74% (95% CI: 62 – 88%) and 72% (95% CI: 60 – 86%), respectively (**Figure 2B**). Five-year EFS rates by histology were: desmoplastic/nodular 66% (95% CI: 43-100%), anaplastic 20% (95% CI: 6-69%), classic 55% (95% CI: 36-84%), or other/undefined 69% (95% CI: 56-84%) (**Figure 2C**). Five-year OS rates by histology were: desmoplastic/nodular 74% (95% CI: 52 – 100%), anaplastic 30% (95% CI: 12 – 77%), classic 54% (95% CI: 34 – 83%), or other/undefined histology 71% (95% CI: 58 – 86%) . M-stage information was only available for those diagnosed post-2008; in this subgroup, the 5-year EFS for those with no metastases at diagnosis (M0) was 54% (95% CI: 36 – 81%) and for those with observed metastases (M1+) was 13% (95% CI: 2 – 78%) **(Figure 2D).** Lastly, the five-year OS rate for residual tumors less than 1.5cm2 was 50% (95% CI: 32 – 79%) and 44% (95% CI: 26 – 77%) for residual tumors greater than 1.5cm2.

Prognostic variables

We utilized Cox proportional hazard modeling to determine factors that may have impacted survival in the study population (**Table 4**). On univariate analysis, three variables were identified that negatively affected EFS and OS in our cohort: anaplastic histology [compared to desmoplastic; OS: HR=3.5 (95% CI: 1.1 – 10.8), p=0.03; EFS: HR=3.4 (95% CI: 1.1 – 10.4), p=0.03], presence of metastasis at diagnosis [OS: HR=3.4 (95% CI: 1.3 – 9.1), p=0.01; EFS: HR=4.4 (95% CI: 1.6 – 11.7), p=0.003], and treatment post-2008 [OS:

HR=2.5 (95% CI: 1.3 – 4.8), p=0.01; EFS: HR=2.5 (95% CI: 1.3 – 4.9); p=0.01]. Large residual tumors were not associated with decreased OS [HR=1.3 (95% CI: 0.6 – 3.1), p=0.52] or EFS [HR=1.4 (95% CI: 0.6 – 3.3); p=0.44]. No differences in survival were observed based on risk stratification [OS: HR=2.0 (95% CI: 0.8 – 4.1), p=0.13; EFS: HR=2.2 (95% CI: 0.9 – 5.5), p=0.09].

Discussion

In this retrospective study, we sought to understand the clinical presentation, treatment, and outcomes for patients diagnosed with medulloblastoma between the ages of three and fifteen years old in Peru, a LMIC between 1997 and 2013, as well as the barriers affecting their survival. Peru is a South American country with a population of over 30 million. Peru is an upper middle-income country that demonstrated large economic growth over the last few years, but was defined as a LMIC during our study period of 1997-2013 according to World Bank criteria (www.worldbank.org). Data collected by the Pan American Health Organization (PAHO) demonstrates that Peru is an example of how advances in health care have decreased mortality due to communicable disease or other preventable diseases while mortality due to malignancy remains relatively unchanged (www.PAHO.org ; **Supplemental Figure 1**).

While the survival rates for average risk medulloblastoma are approaching 80-90% in HIC, survival rates in our study, as well as those in other LMIC suggest areas that can be addressed that will allow for improvement in survival rates in pediatric medulloblastoma in Peru[7, 8, 10, 21]. Univariate analysis demonstrated that histologic sub-type, presence of metastasis at diagnosis, and treatment post-2008 all negatively affected outcomes in our study (**Table 4**). The incompleteness of data pre-2008 could adversely affect comparisons between the two time periods and limited our ability to perform multivariate analysis. The statistically significant decrease in survival for patients with anaplastic subtype or metastasis at diagnosis is consistent with other studies in HIC[22, 23]. Extent of resection was not assessed pre-2008 and rates of GTR were lower in the post-2008 cohort compared to rates of GTR in HIC studies. The extent of resection was not found to be statistically associated with an improved or worse survival outcome in this cohort, which is unexpected given that extent of resection is a clinically important prognostic variable in most HIC studies [15, 16, 18-20, 22]. We hypothesize that the large percentage of our cohort with residual tumor > 1.5cm2 (50% post-2008) contributed to a decreased OS in our cohort compared to studies performed in HIC and could be why gross residual > 1.5cm2 was not associated with worse outcomes in this study. There may be other several factors that contributed to increased numbers of patients with large residuals in our patient population: 1) lack of pediatric-trained neurosurgeons, 2) lack of necessary equipment at facilities where the surgeries took place ie: operative microscopes, or 3) delayed presentation leading to larger primary tumor bulk at diagnosis. Indeed, even in HIC, it has been suggested that higher rates of GTR are obtained when resection is performed by a pediatric-trained neurosurgeon versus a general neurosurgeon [24]. Further analysis of neurosurgical resources in LMIC such as Peru are warranted, however, we do recognize that the prognostic significance of GTR in HIC studies has recently been called into question once controlled for molecular subgrouping[20, 25, 26]. The etiology underlying worse outcomes post-2008 remains unclear. A possible explanation could be the increase of surgeries performed outside INEN and a subsequent delay in referral for treatment leading to the patients presenting with large, difficult to resect tumors and metastasis.

While resection is a critical aspect of medulloblastoma management, having prompt access to radiation therapy planned and administered by specialized radiation oncology facilities and subspecialists also affect the outcome [27]. Given that delays in initiating radiation therapy have been demonstrated to lead to inferior outcomes in medulloblastoma [23, 28], recent treatment protocols state that radiation therapy should begin no later than 28-31 days after surgery [16, 17]. We found that 39 patients (40%) began radiation therapy after 50 days (**Table 3**). Additionally, limited or no access to pediatric trained neuro-oncologists and chemotherapeutic agents may also negatively impact patient outcomes[29]. While pediatric oncologists at the time of this analysis had no specific training in pediatric neuro-oncology, the chemotherapy regimens used both pre- and post- 2008 were similar to those used in HIC [17] and the chemotherapy agents were available.

In addition to surgery, radiation, and chemotherapy, having prompt and accurate MR imaging for pre-operative, and post-operative staging is crucial for management of medulloblastoma. Indeed, in our study,

timing to MRI was a variable that may have affected our statistical analysis. No patient had an MRI done within a 48-hour post-operative window used in HIC to assess extent of resection more accurately. Furthermore, in this cohort, post-operative imaging was only completed in 38/89 patients, all of them in the post-2008 treatment cohort. Even if post-operative MRI could have been obtained quickly, neuro-radiologist with expertise in pediatric neuro-oncology were not available during this time period in Peru. As a testament to the importance of neuro-radiographical assessment during medulloblastoma management, in the landmark study which defined the current standard of care for management of medulloblastoma, radiographical inaccessibility was one of the statistically significant prognostic variables for EFS[17].

As the range of diagnostic techniques broadens and treatment regimens become increasingly designed based on the molecular landscape of pediatric tumors, it is important to remember that approximately 80% of the world's children with cancer are not benefiting from these advances. Given the recent consensus statement and World Health Organization (WHO) guidelines incorporating molecular subtyping into risk stratification for medulloblastoma [30], the inability to perform molecular and signal transduction specific immunohistochemistry may hamper the ability of oncologists in LMIC to accurately risk-stratify their patients. Aside from adding prognostic data, molecular analysis of CNS tumors has proven an important adjunct to arriving at the correct diagnosis. Without the aid of molecular techniques, small round blue tumors of the CNS can be misdiagnosed, resulting in skewing of survival curves and response to treatment. A retrospective molecular analysis from Children's Oncology Group Trial ACNS 0332 of 31 patients with institutionally diagnosed CNS primitive neuroectodermal tumors or medulloblastomas found that 22 patients (71%) were actually other disease entities such as high-grade glioma, atypical teratoid rhabdoid tumors, or ependymomas [31].

Consortiums between LMIC and HIC could potentially aid in improving outcomes for medulloblastomas at INEN. The Latin American Brain Tumor Board (LATB) a weekly multi-disciplinary pediatric neuro oncology-specific teleconference connects institutions from Latin America with those in Canada, Spain, and the United States. The LATB is an example of how collaborative efforts between HIC and LMIC can improve care by giving real-time recommendations to oncologists in LMIC institutions [32]. In summary, outcomes for medulloblastoma patients treated at the INEN from 1997-2013 were inferior compared to outcomes obtained in HIC studies. Some of the barriers identified in this study, which have impeded improved survival at INEN, have been addressed since the conclusion of this study, future analysis will be needed to evaluate the impact of these interventions on patient survival. The challenge of improving survival for Medulloblastomas at INEN is not based on more toxic treatments, but received timely radiotherapy and chemotherapy after maximal safety surgery, and creation on local multidisciplinary Pediatric Neuro Oncology Team, the combination of international efforts such as the LATB and the strengthening of networking and resource sharing among neighboring countries as in Central America are good strategies, that has been successfully demonstrated outstanding results in other Regions.[4].

Conflicts of interest:

Dr. Diaz and Dr. Garcia reports support from Merck Shape & Dome (MSD) not related to the present study. The rest of the coauthors have nothing to disclose. The rest of the authors have nothing to disclose.

Data Availability Statement : The data that support the findings of this study are available from the corresponding author upon reasonable request.

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FIGURE 1 : Geographical assessment of patient location in Peru by City.

FIGURE 2 : Kaplan Meier curves for this study. A) OS and EFS for all patients. B) EFS based on treatment period. C) EFS based on histology. D) EFS based on Metastasis at diagnosis.

TABLE 1 Resources for Pediatric Neuro Oncology

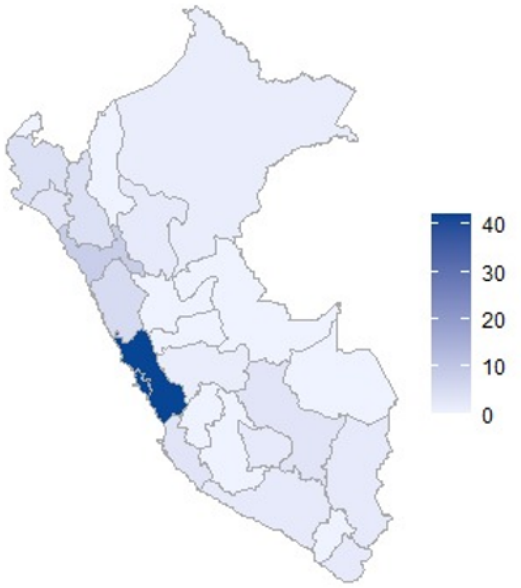
TABLE 2 Demographics and patient characteristics

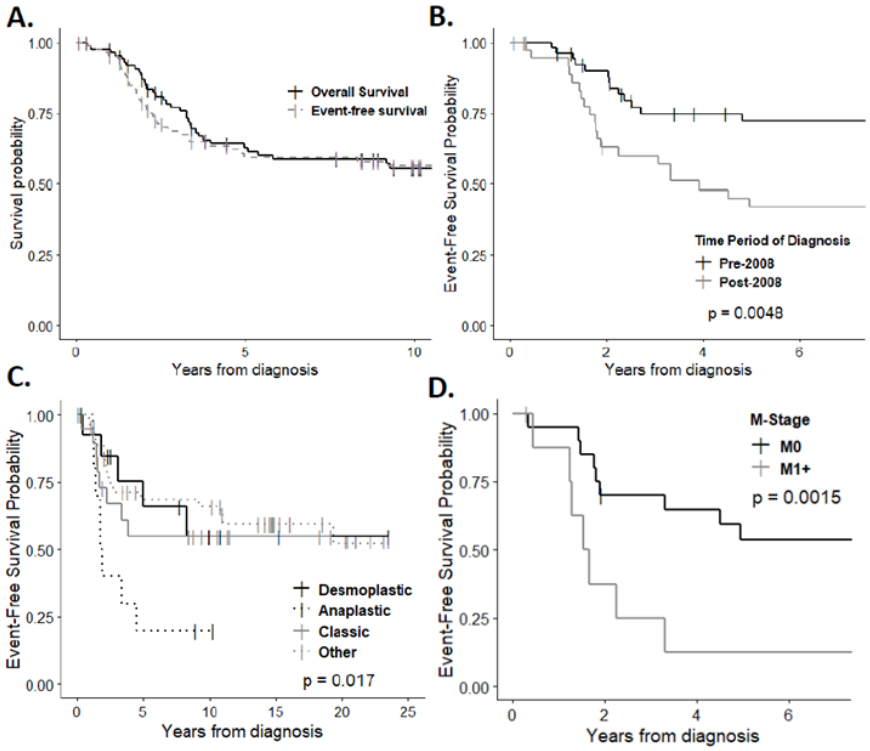
TABLE 3 Clinical management and pathology

TABLE 4 Factors affecting overall and event-free survival

SUPPLEMENTAL TABLE 1 : Availability of Immunohistochemistry for the two periods of treatment.

SUPPLEMENTAL FIGURE 1 : Causes of childhood mortality for ages 1-9 were extracted from PAHO database for the years of 1999 and 2015. Causes are identified by their current ICD 10 code and presented as number of deaths per 100,000.





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