# Different prognostic effect of surgery, radiation and chemotherapy in pediatric medulloblastoma less and over three years old: A Surveillance, Epidemiology, and End Results (SEER) analysis

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## Abstract

# Introduction

To clarify the prognostic value of extent of surgical resection, radiation and chemotherapy in pediatric medulloblastoma patients < 3 years old and ≥ 3 years old.

# Methods

We used the Surveillance, Epidemiology, and End Results program to identify 1,495 pediatric patients diagnosed between 1973 and 2016 with medulloblastoma. Patients with incomplete or unknown clinical information were excluded. Basic characteristics between patients < 3 years old and ≥ 3 years old were compared. Then, we used Cox regression to investigate the impact of extent of surgical resection, radiation and chemotherapy on patient outcome.

# Results

Gross total resection only significantly improved patient outcome in those ≥ 3 years old, and radiation independently correlated to better OS and PFS in patients ≥ 3 years old (all $p < 0.05$). However, chemotherapy only benefited patient outcome in those < 3 years old (all $p < 0.05$). Furthermore, in those ≥ 3 years old patients underwent surgical procedures, radiation alone confer survival benefit only in those received gross total resection ($p < 0.05$) but not in partial resection or biopsy ($p > 0.05$). Notably, adjuvant radiation plus chemotherapy largely improved patient survival independent of extent of resection ($p < 0.05$).

# Conclusions

The extent of resection should be differentially considered and applied between pediatric medulloblastoma patients < 3 years old and ≥ 3 years old, so are the adjuvant radio- and chemo-therapies.

## Introduction

Medulloblastoma is the most common malignant brain tumors in children, comprising for nearly 20% of pediatric brain tumors and 40% of all pediatric posterior fossa tumors [1–3]. The main treatments for pediatric medulloblastoma are maximal safe surgical resection, craniospinal radiation (CSI) and systemic chemotherapy [3, 4]. Due to most common occurrence in brainstem and cerebellum, aggressive surgical resection may be associated with increased postsurgical complications, such as neurologic morbidity and cerebellar mutism. The survival benefit of gross total resection (GTR) is controversial in the literature, which some identify GTR is an independent prognostic factor [5–7], but others do not [8–10].

Current clinical risk stratification of medulloblastoma is the main reference for postsurgical therapy, and the stratification separates children into average risk and high-risk strata. High-risk disease is defined by age < 3 years, subtotal resection (residual tumor ≥ 1.5 $cm^2$), or metastasis at diagnosis [5, 7, 11–14]. Maximal safe surgical resection followed by risk adapted CSI and systemic chemotherapy have produced the best survival benefit for pediatric patients aged between 3 and 18 years [12, 13, 15, 16]. However, little success is achieved in infant and younger children under 3 years of age. Concerns of neurocognitive impairment limiting the application of CSI in those younger patients may account for the limited benefit. In addition, it is not always available to received risk-adapted and “standard” therapies due to patient adherence and limited resources, especially in low and middle income countries and areas [3, 17]. Thus, it is important to identify possible prognostic factors in pediatric patients under 3 years of age.

In present study, we used the Surveillance, Epidemiology, and End Results (SEER) database to identify prognostic factors in pediatric medulloblastoma patients. We firstly investigated the frequency of received treatments including surgery, radiation and chemotherapy in medulloblastoma patients with different ages and found that the rate of radiation in patients with age of 0, 1 and 2 years is significantly lower than their counterparts with other ages. Then, we classified pediatric medulloblastoma patients into < 3 years group and ≥ 3 years group, and compared the difference of basic characteristics and outcomes between these two groups. Lastly, we selected multiple parameters to identify prognostic factors by Cox regression in < 3 years group and ≥ 3 years group, respectively.

# Methods

Patient cohort

We used the SEER database to identify 1,495 pediatric patients diagnosed between 2000 and 2016 with medulloblastoma, which were specified by four specific ICD-O-3 codes: 9470/3-medulloblastoma, NOS, 9471/3-desmoplastic nodular medulloblastoma, 9472/3-medullomyoblastoma and 9474/3-large cell medulloblastomas, as previously reported. The age of pediatric patients defined as younger than 18 years old, and patients age of < 1 year was defined as 0 year old. This study was conducted in accordance with the policies of the Scientific Ethics Committee of SEER program and Sun Yat-sen University.

Study design

As determined by SEER, race was classified as white, African American and others. The extent of surgical resection was defined as: no surgery, biopsy, partial resection (PR) and gross total resection (GTR), which were created to surgical procedure codes as previously described [18]. PR and GTR were defined as surgery performed. Patients received any type of radiation including beam radiation, radioactive implants, raioisotopes, or combinational radiotherapy were classified as radiation used. Patients were excluded if clinical information including race, surgery, tumor resection rate, radiation, histology, chemotherapy and survival months was incomplete or unknown, leaving 939 patients in the final cohort. Overall survival

(OS) was defined as the time from the diagnosis until death from any cause, and progress free survival (PFS) was defined as the time from diagnosis until death caused by the original brain cancer.

# Statistical Analysis

Baseline patient characteristics were presented as percentages and compared with Chi-Squared test. Multivariable analyses with the Cox proportional-hazards model were used to assess the impact of multiple covariates on patients' OS and PFS. And the selected covariates were age, sex, surgical resection, radiation and chemotherapy. To further clarify the role of radiation and chemotherapy in pediatric medulloblastoma, adjuvant treatment strategy was redefined as none, chemotherapy, radiation, and radiation plus chemotherapy, and then was put into Cox regression analysis. Statistical analysis was carried out using SPSS 22.0 (Chicago, IL, USA). A $p$ value $< 0.05$ was considered statistically significant.

# Result

A total of 939 patients were included after exclusion of 556 patients. As shown in Fig. 1, most of the patients aged between 0 to 10 years old. Of these cohort of patients, the number of patients with medulloblastoma, NOS (9470/3), desmoplastic nodular medulloblastoma (9471/3), medullomyoblastoma (9472/3) and large cell medulloblastomas (9474/3) were 784, 101, 3 and 51, respectively (Fig. 1 and Table 1). Due to the concerns of adverse effects, each treatment was differentially applied in every age strata. Only 13.2%, 27.8% and 35.2% of patients in age of 0, 1 and 2 years received radiation, which were significantly lower than that in other age strata, ranging from 74.8–100% (Fig. 2). However, patients in each age strata received comparable chemotherapy and surgical resection (Fig. 2).

Table 1
Basic characteristics of medulloblastoma patients with age of < 3 years and ≥ 3 years

| | < 3 years (n = 196) | ≥ 3 years (n = 743) | *p* value |
|---|---|---|---|
| **Sex (Male), n(%)** | 108(55.1) | 479(64.5) | 0.016 |
| **Race, n(%)** | | | 0.397 |
| **White** | 161(82.1) | 629(84.7) | |
| **Black** | 15(7.7) | 60(8.1) | |
| **Others** | 20(10.2) | 54(7.3) | |
| **Histology, n(%)** | | | < 0.001 |
| **9470** | 143(73.0) | 641(86.3) | |
| **9471** | 45(23.0) | 56(7.5) | |
| **9472** | 0(0) | 3(0.4) | |
| **9474** | 8(4.1) | 43(5.8) | |
| **Surgical resection, n(%)** | | | 0.088 |
| **No surgery** | 17(8.7) | 44(5.9) | |
| **Biopsy** | 47(24.0) | 178(24.0) | |
| **Partial resection** | 41(20.9) | 115(15.5) | |
| **Gross total resection** | 91(46.4) | 406(54.6) | |
| **Radiation, n(%)** | 53(27.0) | 631(84.9) | < 0.001 |
| **Chemotherapy, n(%)** | 165(84.2) | 641(86.3) | 0.456 |
| **6-month survival, n(%)** | 157(80.5) | 700(94.7) | < 0.001 |
| **1-year survival, n(%)** | 135(69.2) | 656(88.8) | < 0.001 |
| **3-year survival, n(%)** | 113(57.9) | 553(74.8) | < 0.001 |
| **5-year survival, n(%)** | 103(52.8) | 502(67.9) | < 0.001 |
| **10-year survival, n(%)** | 56(28.7) | 255(34.5) | 0.127 |

9470/3, medulloblastoma, NOS; 9471/3, desmoplastic nodular medulloblastoma; 9472/3, medullomyoblastoma; 9474/3, large cell medulloblastomas; PR, partial resection; GTR, gross total resection. The same for the following tables.

Hence, we classified the cohort of patients into < 3 years group and ≥ 3 years group and compared the difference of basic characteristics. Consistent to the previous report that the incidence of

medulloblastoma is higher in male, and even higher in ≥ 3 years group (55.1% vs 64.5%, $p = 0.016$) (Table 1). There are more desmoplastic nodular medulloblastoma cases (23.0% vs 7.5%), lower rate of GTR (46.4% vs 54.6%) and less radiation (27.0% vs 84.9%, $p < 0.001$) in < 3 years group. However, patients in both groups received comparable chemotherapy (84.2% vs 86.3%, $p = 0.456$). As expected, the outcome of patients younger than 3 years old was much worse compared to their counterparts, and the rate of 6-month survival, 1-year survival, 3-year survival, 5-year survival and 10-year survival was 80.5% vs 94.7% ($p < 0.001$), 69.2 vs 88.8% ($p < 0.001$), 57.9% vs 74.8% ($p < 0.001$), 52.8% vs 67.9% ($p < 0.001$) and 28.7% vs 34.5% ($p = 0.127$) between those two groups, respectively (Table 1).

To identify prognostic risk factors, parameters including age, sex, histology, surgical resection, radiation and chemotherapy were selected for Cox regression analysis for both groups. We found that patients age, chemotherapy independently benefit patient OS ($p < 0.001$) and PFS($p = 0.008$), however, radiation and extent of resection did not in < 3 years group (Table 2). For those patients ≥ 3 years patients, the more frequently applied radiation significantly prolonged patient OS and PFS (all $p < 0.001$) (Table 3). Unlike < 3 years group, surgery performed could significantly prolong patient OS ($p < 0.05$) (Table 3). However, chemotherapy did not benefit patient outcome ($p > 0.05$) (Table 3). In both groups, desmoplastic nodular medulloblastoma negatively correlated to patient outcome compared to medulloblastoma, NOS ($p < 0.05$) (Tables 2 and 3).

Table 2
Hazard Ratios for overall survival and progress free survival in medulloblastoma patients aged < 3 years old

| | **OS** | | **PFS** | |
|---|---|---|---|---|
| | p **value** | **95% CI** | p **value** | **95% CI** |
| **Age** | 0.152 | 0.808(0.604–1.081) | 0.868 | 1.030(0.731–1.450) |
| **Sex** | 0.629 | 1.117(0.712–1.753) | 0.534 | 1.180(0.700-1.989) |
| **Resection (No surgery)** | | | | |
| **Biopsy** | 0.375 | 0.683(0.294–1.587) | 0.734 | 0.826(0.273–2.496) |
| **PR** | 0.494 | 0.750(0.329–1.711) | 0.789 | 1.154(0.404–3.297) |
| **GTR** | 0.664 | 0.841(0.385–1.838) | 0.843 | 1.109(0.399–3.082) |
| **Radiation** | 0.172 | 0.667(0.373–1.192) | 0.167 | 0.634(0.332–1.210) |
| **Chemotherapy** | < 0.001 | 0.330(0.179–0.609) | 0.008 | 0.362(0.171–0.767) |
| **Histology (9470)** | | | | |
| **9471** | 0.023 | 0.456(0.232–0.897) | 0.028 | 0.406(0.182–0.906) |
| **9474** | 0.006 | 2.938(1.367–6.311) | 0.008 | 3.335(1.362–8.168) |

Table 3
Hazard Ratios for overall survival and progress free survival in medulloblastoma patients aged ≥ 3 years old

| | OS | | PFS | |
|---|---|---|---|---|
| | p **value** | **95% CI** | p **value** | **95% CI** |
| **Age** | 0.210 | 0.979(0.947–1.012) | 0.199 | 0.976(0.940–1.013) |
| **Sex** | 0.919 | 1.014(0.780–1.317) | 0.224 | 0.829(0.613–1.122) |
| **Resection (No surgery)** | | | | |
| **Biopsy** | 0.005 | 0.480(0.287–0.803) | 0.66 | 0.854(0.422–1.727) |
| **PR** | 0.049 | 0.587(0.344–0.999) | 0.868 | 1.063(0.518–2.182) |
| **GTR** | 0.001 | 0.449(0.277–0.729) | 0.463 | 0.776(0.292–1.520) |
| **Radiation** | < 0.001 | 0.394(0.269–0.578) | < 0.001 | 0.405(0.264–0.621) |
| **Chemotherapy** | 0.722 | 0.927(0.611–1.407) | 0.923 | 1.024(0.631–1.662) |
| **Histology (9470)** | | | | |
| **9471** | 0.082 | 0.568(0.301–1.074) | 0.146 | 0.607(0.310–1.189) |
| **9472** | 0.162 | 2.731(0.669–11.150) | 0.070 | 3.701(0.900-15.215) |
| **9474** | 0.008 | 1.878(1.180–2.988) | 0.003 | 2.092(1.280–3.420) |

Since less concerns of adverse effect of adjuvant radiation and chemotherapy in patients over 3 years old, we further clarified the survival benefit of radiation and chemotherapy in those patients who underwent biopsy, PR or GTR. Parameters including age, sex, histology and adjuvant therapy were selected for Cox regression. Radiation alone did improve patient outcome in those received PR or GTR, but not in those received biopsy (Tables 4 and 5). Surprisingly, chemotherapy alone could not benefit patient OS ($p > 0.05$) and PFS ($p > 0.05$) neither in those underwent biopsy, PR or GTR (Tables 4 and 5). And radiation could only significantly prolong patient OS ($p = 0.011$; OR 0.230; 95% CI, 0.074 to 0.716) and PFS ($p = 0.017$; OR 0.206, 95% CI, 0.056 to 0.754) in those received GTR. Noteworthy, radiation plus chemotherapy significantly improved patient outcome even more (Tables 4 and 5).

Table 4
Hazard Ratios of adjuvant therapy for overall survival in medulloblastoma patients ≥ 3 years old underwent surgery

| Adjuvant therapy | Biopsy | | PR | | GTR | |
|---|---|---|---|---|---|---|
| | p value | 95% CI | p value | 95% CI | p value | 95% CI |
| Chemotherapy | 0.921 | 1.060 (0.332–3.386) | 0.803 | 0.799 (0.137–4.663) | 0.334 | 0.673 (0.301–1.504) |
| Radiation | 0.654 | 0.738 (0.196–2.785) | 0.975 | | 0.011 | 0.230 (0.074–0.716) |
| Radio- and Chemo-therapy | 0.078 | 0.430 (0.168–1.099) | 0.039 | 0.381 (0.153–0.952) | < 0.001 | 0.271 (0.148–0.496) |

Table 5
Hazard Ratios of adjuvant therapy for progress free survival in medulloblastoma patients ≥ 3 years old underwent surgery

| Adjuvant therapy | Biopsy | | PR | | GTR | |
|---|---|---|---|---|---|---|
| | p value | 95% CI | p value | 95% CI | p value | 95% CI |
| Chemotherapy | 0.624 | 1.364 (0.394–4.726) | 0.965 | 0.962 (0.164–5.641) | 0.263 | 0.596 (0.241–1.474) |
| Radiation | 0.882 | 0.899 (0.221–3.662) | 0.977 | | 0.017 | 0.206 (0.056–0.754) |
| Radio- and Chemo-therapy | 0.118 | 0.433 (0.151–1.238) | 0.045 | 0.369 (0.140–0.977) | < 0.001 | 0.273 (0.140–0.529) |

# Discussion

In present study, we firstly found that there was more desmoplastic nodular medulloblastoma cases (20.9%) in patients < 3 years (Fig. 1 and Table 1), however, which is lower than 44% in the previous reports [14]. Secondly, radiation was less frequently applied in patients < 3 years, which is consistent to the clinical practice of reduced or delayed application of radiation in those patients due to concerns of

neurocognitive impairment [19, 20]. Thirdly, we identified that patients < 3 years was really in high risk compared to patients ≥ 3 years with lower 6-month, 1-year, 3-year and 5-year survival rate. Differential epidemiological characteristics, such as age and histology, and application of radiation as shown in Table 1 might account for survival difference between patients < 3 years old and ≥ 3 years old. Indeed, before use of CSI, medulloblastoma remains incurable in older children even with GTR [4, 21].

In the literature, the benefit of GTR remains controversial. Albright et al [6] and Zeltzer et al [7] reported survival benefit of GTR over PR or biopsy in patients > 3 years old, however, no significance was found in Akyuz's study with patients age of 0 to 18 years old [9] and in Evans's study with patients age of 2 to 16 years old [10]. The above studies implied that age might affect significance of GTR in survival. In a large retrospective study, Thompson et al found significant interaction between age and extent of resection, however, they did report overall and progress-free survival benefit of GTR compared to near total resection and subtotal resection in patients < 3 years old [5]. Notably, the prognostic benefit of increased extent of resection was attenuated when molecular subgroup affiliation is taken into account [5]. Similarly, the present study demonstrated that GTR did not confer OS and PFS benefit in patients < 3 years old (Table 2). However, GTR showed OS benefit but no PFS benefit in ≥ 3 years old group (Table 3).

It is well established that radiation alone could largely improve patient perspective and cure the disease [4, 21]. Early studies elicited that chemotherapy alone could prolong tumor free survival in younger children less than 18 months of age [22]. For those patients aged < 5 years old, Grill et al proved that conventional chemotherapy alone was sufficient to cure patients who had GTR, but not those with incompletely resection or metastatic medulloblastoma [20]. The present study identified that chemotherapy but not radiation significantly improved OS and PFS in younger patients < 3 years old (Table 2), however, the OS and PFS benefit of chemotherapy and radiation was inverted in those patients ≥ 3 years old (Table 3). Different sensitivity of histological subtypes to chemotherapy might account for the difference between patients < 3 years old and ≥ 3 years old [23, 24], since there are more desmoplastic nodular medulloblastoma cases in < 3 years old patients. Furthermore, in those patients ≥ 3 years old and underwent surgical procedures, the benefit of radiation alone largely depends on the extent of resection (Tables 4 and 5). It is worth noting that adjuvant radiation together with chemotherapy largely improves patient outcome even in those underwent partial resection (Tables 4 and 5).

With the introduction of molecular diagnosis by the 2016 WHO classification of central nervous system tumor [25], different molecular subtype and origin of medulloblastoma determine the sensitivity to chemo-, radio- or targeting therapy [4, 5, 26, 27]. Hence, pathological diagnosis from surgical procedures is highly recommended in the treatment of pediatric medulloblastoma. Due to apparent reasons, the epidemiology of molecular subtype and its impact on the outcome of pediatric medulloblastoma is out of the scope of the study.

Due to limited cases, we were unable to further investigate the survival benefit of radiation and chemotherapy in medulloblastoma patients less than 3 years old who received biopsy, PR or GTR. Also, the study is subject to inherent limitations of retrospective study. The treatment patterns might vary from

each patient and doctor, and the “standard” treatments including radio- and chemo- therapy differ from each year or each version of guideline. Moreover, the further details of radiation or chemotherapy are largely unknown and might impact the results of present studies and cause bias.

Notwithstanding these limitations, data from present study demonstrates that the extent of surgical resection confer overall survival benefit in those ≥ 3 years old patients but not in those < 3 years old. Chemotherapy shows OS and PFS benefit in those ≥ 3 years old patients but not in those < 3 years old, however, radiation shows inverted effect between those two populations. Moreover, adjuvant radiation plus chemotherapy largely is the most effective adjuvant treatment for those underwent tumor resection. In conclusion, the extent of resection should be differentially considered and applied between pediatric medulloblastoma patients < 3 years old and ≥ 3 years old, so are the adjuvant treatments.

# Declarations

The authors declare that the work described is original work and is not under review by any other journal. The data access is approved by the SEER program and the usage is in accordance to the policies of SEER program.


### Funding

Not applicable.


### Conflicts of interest

There is no conflict of interest exits in the submission of this manuscript.

### Availability of data and material

In the present study, all data were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Researchers can request and get access to the data at https://seer.cancer.gov.

### Authors’ contributions

Zhong Deng and Tuo Wang designed and conducted this research. Yichang Wang and Xixi Li contribute equally to the present work. Yichang Wang and Xixi Li collected and analyzed all data. Hongxi Tang and Jia Yang contributed the Tables and Figures composition. Zhong Deng and Tuo wang wrote and revised the manuscript together.

### Ethics approval

The study is conducted in accordance with the policies of the Scientific Ethics Committee of Sun Yat-sen University.

### Consent to participate

Not applicable.

### Consent for publication

All the authors have read the final version of this manuscript and approved for publication.

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# Figures

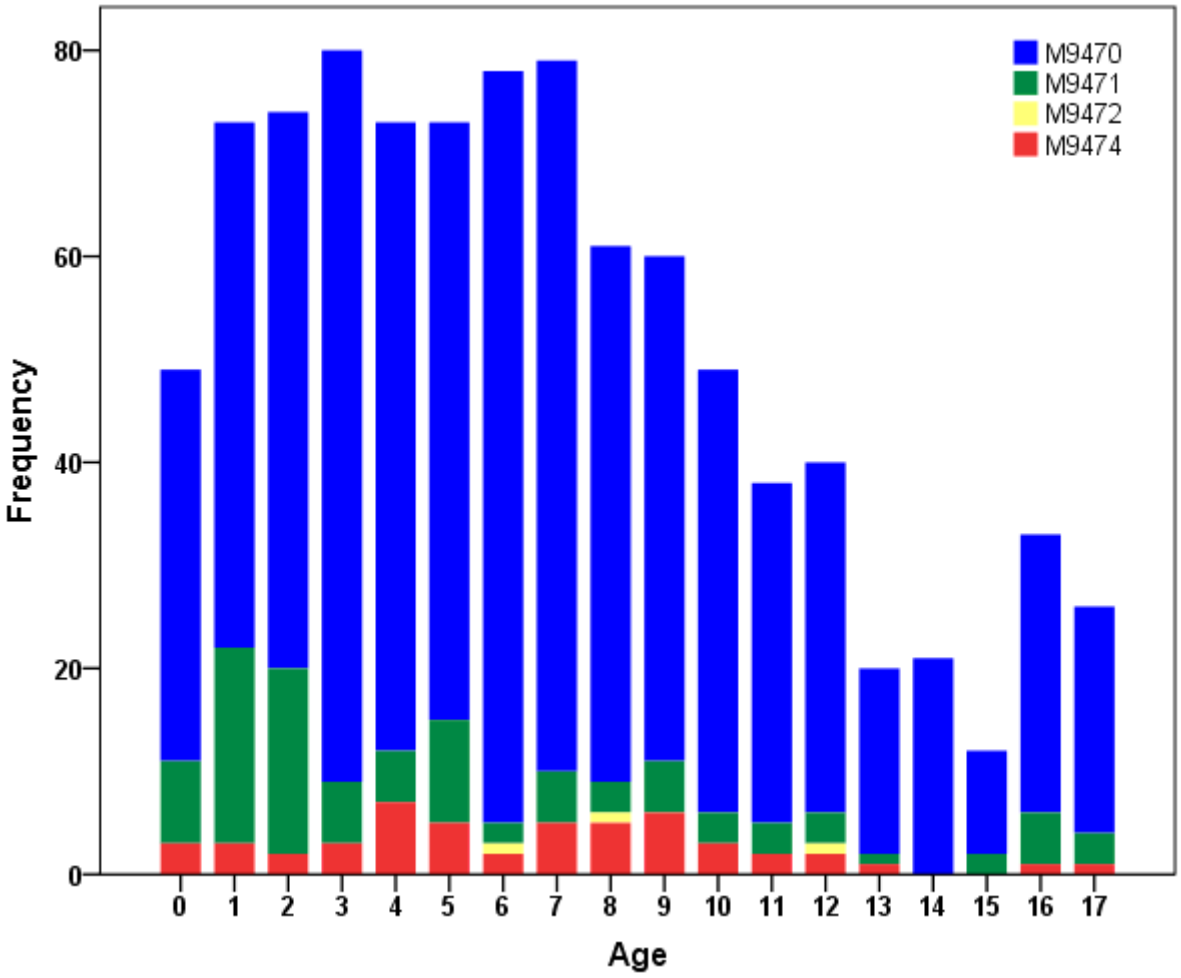
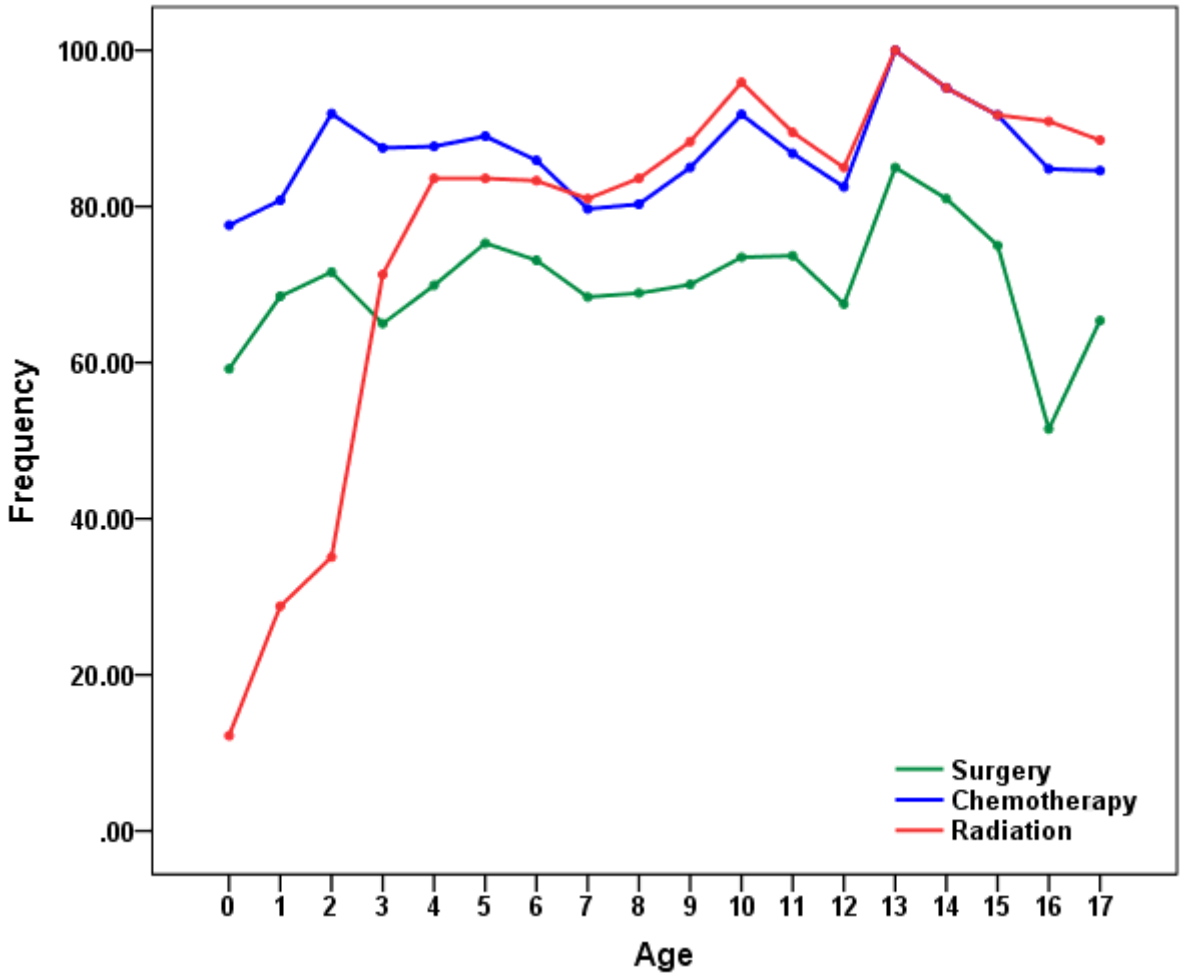



**Figure 1**

Histogram represents the frequency of each subtype of medulloblastoma in every age strata. Medulloblastoma ICD-O-3 codes: 9470, medulloblastoma, NOS; 9471, desmoplastic nodular medulloblastoma; 9472, medullomyoblastoma; 9474, large cell medulloblastomas.




## Figure 2

Line chart shows the percent of medulloblastoma patients received surgery, chemotherapy and radiation in every age strata.