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A Phase II Study (CCG 9931) of Pre-Radiotherapy Chemotherapy Followed by Hyperfractionated Radiotherapy for Newly Diagnosed High Risk Medulloblastoma/PNET: A Report from the Children's Oncology Group

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Abstract

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Purpose—Children with high risk medulloblastoma and non-cerebellar PNET's were treated on a phase II study of pre-radiotherapy chemotherapy (CHT) followed by high dose, hyperfractionated craniospinal radiotherapy (CSRT). The protocol objectives were to verify feasibility and monitor progression-free (PFS) and overall survival (OS).

Methods and Materials—Eligibility criteria included age >3 years at diagnosis, medulloblastoma with either high M stage and/or >1.5 cm^2 post-op residual disease and all patients with non-cerebellar PNET. Treatment was initiated with 5 alternating monthly cycles of CHT [A (cisplatin, cyclophosphamide, etoposide and vincristine, B (carboplatin and etoposide), A, B and A] followed by hyperfractionated CSRT (40 Gy) with a boost to the primary tumor (72 Gy) given in twice daily 1 Gy fractions.

Results—The valid study group consisted of 124 patients whose median age at diagnosis was 7.8 years. Eighty-four (68%) patients completed the entire protocol within the study guidelines of 9 months and the median time to complete CSRT was 1.6 months. Major reasons for failure to complete CHT included progressive disease (17%) and toxic death (2.4%). The 5-year PFS and OS were 43 ± 5% and 52 ± 5%. No significant differences were detected in subset analysis related to response to CHT, site of primary tumor, post-op residual disease or M-stage.

Conclusions—The feasibility of this intensive multi-modality protocol was confirmed and response to pre-RT CHT did not impact on survival. Survival data from this protocol can not be compared to other studies, given the protocol design.

Keywords

PNET; Medulloblastoma; High risk; Hyperfractionated radiotherapy; Pre-radiation chemotherapy

INTRODUCTION

The prognosis of children with primary CNS primitive neuroectodermal tumors (PNET) such as medulloblastoma, pineoblastoma and cerebral PNET is related to several clinical and pathological criteria. High risk criteria include metastatic disease at diagnosis (M+), < 3 years of age at diagnosis, incompletely resected primary tumor (> 1.5 cm^2 residual), a non-cerebellar primary tumor site and unfavorable histology. The 5 year survival varies markedly between standard risk and high risk disease (>75% vs. <40%). [1] [2]

Improvements in outcome for children with high risk disease in children > 3 years of age may occur with modifications of doses and schedule of CSRT and CHT. The dose of myelosuppressive CHT may be more safely augmented prior to CSRT and the neurotoxicity of certain drugs such as cisplatin and methotrexate is reduced. [3]. [4]. [5]. [6]. A number of pilot studies have been conducted using pre-RT CHT for patients with PNET and there is considerable controversy regarding optimum duration and drug selection.[7] The efficacy of RT is usually dose dependent and higher doses can be administered theoretically more safely using hyperfractionated treatment schedules.[8,9] There have also been several small pilot studies using hyperfractionated CSRT immediately following surgery. [9,10]

We report the results of a phase II Children's Cancer Group pilot study (CCG 9931) consisting of 5 monthly courses of CHT followed by hyperfractionated CSRT. The CHT consisted of 2 alternating drug combinations active against PNET.[11,12] The goals of this group-wide protocol were: 1. To determine its feasibility with close monitoring of disease progression during CHT, toxicity and delays in the delivery of protocol CHT and CSRT; 2. To determine if responses to CHT influences survival and 3. To monitor progression-free (PFS) and overall survival (OS).

METHODS AND MATERIALS

Patient Eligibility

IRB approval and informed consent were required for all study patients. Protocol inclusion criteria included age ≥ 3 ≤ 22 years at diagnosis and histologically confirmed, previously untreated medulloblastoma or a PNET arising in the brain, brainstem or spinal cord. All medulloblastoma patients had evidence of either residual posterior fossa tumor >1.5 cm^2 and/or CNS metastatic disease (M1–3) whereas all PNET patients were eligible. An extent of disease evaluation was performed which included an enhanced brain and spine MRI preferably within 72 hours after surgery and a lumbar CSF cytology examination within 2–3 weeks after surgery. CSF cytological examination was waived in patients for whom the neurosurgeon felt a lumbar puncture was contraindicated. A bone marrow aspirate and bone scan were optional. Central review of the pathology was performed independently by 2 neuropathologists (LR and DM) and patients were excluded from further analysis if both concurred that the diagnosis of PNET or medulloblastoma was not supportable.

Pre-radiotherapy Chemotherapy

Patients had to begin chemotherapy within 28 days of surgery. Five alternating multi-agent CHT courses were administered every 4 weeks. Regimen A was used for the 1st, 3rd and 5th courses of chemotherapy and consisted of cisplatin (90 mg/M^2, IV) on day 0, etoposide (75 mg/M^2, IV) on days 0, 1 and 2, cyclophosphamide (1.5 gm/M^2 IV) on days 1 and 2, and vincristine (1.5 mg/M^2 IV, max 2.0 mg) on days 0, 7 and 14. G-CSF (5 mg/kg SC) was administered daily for at least 10 days after each course of Regimen A. Regimen B was administered on the 2nd and 4th courses and consisted of carboplatin (400 mg/M^2 IV) on days 0 and 1 and etoposide (75 mg/M^2 IV) on days 0, 1 and 2. Hematologic criteria for initiating the next course consisted of an ANC >750/mm^3 at least 48 hours after discontinuation of G-CSF and a platelet count > 100,000/mm^3. Restaging with gadolinium enhanced MRI of the head and spine was required after the 2nd and 5th courses of chemotherapy CHT or at any time progressive disease was suspected.

Hyperfractionated Radiotherapy

Radiotherapy could be initiated any time during CHT for the following reasons: the emergence of recurrent or progressive disease; a delay > 6 weeks between courses of CHT or if the total duration of CHT exceeded 7 months. Otherwise, radiotherapy commenced 1 month after the completion of CHT following hematologic recovery. Initially, the entire neuroaxis was treated using a hyperfractionated schedule of 1 Gy twice daily, separated by 6–8 hours, to a total dose of 40 Gy. The primary intracranial tumor and intracranial metastasis were boosted to 72 Gy using the same fractionation schedule. The protocol specified if the supratentorial boost encompassed more than 2/3 of the total supratentorial volume, the total dose to the supratentorial boost region should not exceed 60 Gy. Metastases on the spinal cord were boosted to 50 Gy and those in the cauda equina region to 56 Gy.

G-CSF was used during radiotherapy according to the following plan. If the ANC was < 3000/mm3 on Friday, then G-CSF (5 mg/kg SC) was administered daily on Friday, Saturday and Sunday. If the ANC remained below 1000 on Monday, then G-CSF was continued daily during the week with radiotherapy. Radiotherapy was only withheld for an ANC <500. Platelet transfusions were administered for counts < 30,000/mm^3 but radiotherapy was not withheld for thrombocytopenia unless 3 or more platelet transfusions were given within 8 days. Nutritional support (enteral or parenteral) was initiated for weight loss > 10% from baseline.

Neuroimaging

The maximum response during CHT was determined by comparing the baseline brain MRI to one obtained after the 5th course of chemotherapy. Standard response criteria were used employing a 2 dimensional measurement technique of the maximum tumor diameter on the axial enhanced T-1 weighted sequence. Surveillance MRI scans were performed 1 month after completion of RT and then every 4 months for 2 years, every 6 months for 2 years and yearly thereafter. If clinical or radiographic progression was suspected at any time, the patient was completely restaged to include a bone marrow aspirate. As a supportive care measure, the protocol recommended that endocrine exams be performed every 6 months and neuropsychometric exams every 3 years, but this data was neither monitored nor collected.

Statistical Methods and Study Endpoints

The protocol treatment was considered feasible if at least 55% of patients completed the chemotherapy and radiotherapy components within 9 months without incurring a protocol modifying event such as progressive disease during CHT, inordinate delays between courses of CHT or the inability to complete RT. The primary endpoints for statistical analysis included response to CHT, PFS (time from study entry to disease progression/relapse and OS (time from study entry to death from any cause). Nonparametric estimates of PFS and OS probabilities were obtained using the product limit (Kaplan-Meier) estimate with standard errors computed using the Greenwood formula. The log rank test was used in univariate analysis of differences in PFS and OS among patient subgroups. The stratified log rank test was used to correct for effects of other factors related to PFS and OS, such as M-stage, residual and tumor site. All p-values quoted are two-sided [13].

RESULTS

Patient Selection

The study accrued 128 patients over 36 months. Two patients were declared ineligible because they failed to meet on study requirements: no spine MRI (1) and systemic metastases (1). Two other patients had a discrepant pathology diagnosis. Thus, further data analysis was performed on the remaining 124 patients.

Demographics

The median age of this cohort at diagnosis was 7.8(3–20) years. There were 80 males and 44 females with an M/F ratio of 1.8. The primary tumor sites were: cerebellar (85), non-pineal supratentorial (28),, pineal (8) and other (3 - brainstem, pons, leptomeningeal). Three of the 28 patients with supratentorial (non-pineal) and 1 of 8 with a pineoblastoma were M+. Table 1 summarizes the patient demographics by M-stage, site and post-op residual tumor.

Neurosurgical Management

The degree of resection of the primary tumor was: gross total resection – 36; radical(> 90%) resection – 43; partial/subtotal resection – 32 and biopsy – 13. Fifty patients had ≥1.5 cm^2 residual tumor, 19 (38%) of whom were M+. Shunts were placed in 10 patients. Post-op complications occurred in 58 patients consisting of localized wound infections (3), CNS infections (5), pseudomeningocele (11) and hydrocephalus (12). Some patients had multiple complications.

Pre-Radiotherapy Chemotherapy

Treatment related toxicity was monitored for each of the 5 courses of CHT. There were more toxic events during Regimen A. Grade 3–4 infection occurred in 18 patients and all 3 of the 4 treatment related deaths were due to infection. Ninety-two of the 124 (74%) patients completed

the full 5 courses of CHT.. Eighty-two (66%) completed CHT in CCR or response (CR, PR or SD), 9 (7%) developed PD after 5 courses of CHT. One patient's response is unknown. Thirty-two (26%) failed to complete CHT. The reasons included: toxic death (3), PD (21), and withdrawal due to treatment delay or other reasons (8).

Hyperfractionated radiotherapy

Radiotherapy was administered to 88%(109/124) of patients. This included 18(15%) patients who developed PD during CHT and 6 patients who could not complete CHT on schedule. The mean dose delivered to the craniospinal axis was 40 Gy and the boost dose varied by site of the primary tumor (cerebellar/brain/spine: 72/60/50 Gy). The use of supportive care measures during CSRT in 109 patients included G-CSF (62%), corticosteroids (34%), and intravenous (18%) or enteral (15%) nutritional supplements.

Feasibility

An early stopping rule required that at least 11 of the first 20 patients complete CHT and RT within 9 months. Fifteen of the first 20 patients, and ultimately 84 of 124 patients (68%) were able to complete CHT and RT within 9 months satisfying the feasibility objective of 55%. Overall, 85 of 124 patients completed 5 courses of CHT and RT in a median of 6.1 months. The median time to complete CSRT was 1.6 months in the 85 patients who completed the entire protocol therapy. Over 90% completed CSRT in less than 2 months.

Progression-Free and Overall Survival

The median follow-up for the patients who were alive at last contact was 7.9(1.1–11.5) years. Of the 124 eligible patients, 61(49%) have died (58 from disease and 3 from treatment related infection). There were 74 occurrences of PD/relapse; 30 developed progression during protocol therapy and 44 thereafter. The median time to PD was 302 (0 – 3416) days. The patterns of the recurrences were: local only - 31; distant only - 15, local and distant - 16; extra neural only - 2; local and extra neural - 3; second malignancy (glioblastoma) - 1 and unknown - 6. The 5-year PFS and OS are 43 ± 5% and 52 ± 5%. There was no significant difference in survival between those who experienced a CR/CCR compared to a PR/SD/MR (p=0.34) for those patients who completed CHT.

Table 2 shows the 5-year PFS and OS according to site (cerebellar, supratentorial and pineal) and M-stage and post-op residual for cerebellar primaries. No significant differences were found in PFS (p=0.37) or OS (p=0.40) amongst the tumor sites (Figures 1 and 2). Two patients with brainstem PNET's died within 1 year and a patient with leptomeningeal primary remains in continuous remission.

DISCUSSION

CCG protocol 9931 endeavored to verify the feasibility of a very intensive multi-modality treatment of high risk medulloblastoma/PNET in order to improve survival using prolonged (5 months) pre-RT CHT and hyperfractionated, augmented dose craniospinal axis radiotherapy. The feasibility was confirmed by pre-determined study criteria. Although the phase II design prohibits a statistical comparison of survival with other studies, the 5 year survival data (PFS/OS – 43/52%) appears similar to other contemporary, less intensive protocols with similar eligibility criteria.[1] [14]

The preceding Children's Cancer Group phase III high risk study for medulloblastoma/PNET, CCG 921, reported a 5 year PFS in patients with M2–3 or M0 with > 1.5 cm^2 post-op residual tumor of 40% and 54%, resp.. CHT was administered either after conventional CSRT [Regimen A - 8 courses of CCNU, prednisone and vincristine) or in a sandwich fashion as in Regimen

B [before (2 courses of “8-in-1”) and after (6 courses of “8-in-1”)]. Patients receiving Regimen A had a longer PFS (p=.006)[1] The strategy design for CCG 9931 emerged from this experience with the intention of intensifying both pre-RT CHT and radiotherapy.

The rationale of using pre-RT CHT in patients with high risk PNET includes the study of novel treatment regimens in patients with newly diagnosed disease and if effective, the delivery of a patient to radiotherapy with a lower disease burden. Initial reports of pre-RT CHT for medulloblastoma/PNET consisted of small institutional series using single (cyclophosphamide, high dose methotrexate) or multiple agents for 2–3 months prior to RT. [15], [4],[16],[17] In a large cooperative group German study (HIT ’88/’89), 94 patients with both standard and high risk medulloblastoma were treated with 2 monthly cycles of chemotherapy (procarbazine, ifosfamide/mesna, etoposide, high dose methotrexate, cisplatin and cytarabine) prior to CSRT. The objective response rate was 67% and the 5 year PFS for high risk medulloblastoma was 57% in 14 patients.

As a consequence of this encouraging experience, this cooperative group conducted a randomized trial in medulloblastoma patients of all risk groups comparing pre-RT CHT (ifosphamide, etoposide, high-dose methotrexate, cisplatin and cytarabine for 2 cycles) followed by standard CSRT with weekly vincristine vs. standard CSRT followed by adjuvant CHT (8 cycles of cisplatin, CCNU and vincristine). There was no clear cut difference in outcome between the 2 arms but there were more interruptions of CSRT in the pre-RT CHT arm. Patients with high risk disease (M2/3) did poorly in both arms with a 3 year PFS of 30%. [18]

In a similar study (SIOP/UKCCSG PNET-3) conducted in England, 68 patients with high risk medulloblastoma received 4 monthly cycles of vincristine, cyclophosphamide, etoposide and carboplatin followed by standard CSRT. Objective responses to chemotherapy were documented in 73% and 18% developed progressive disease during the pre-RT CHT. However, the 5 year PFS was 34.7%, not very different from prior historical experience with more conventional therapies. An objective response to pre-RT CHT did not confer a survival advantage.[19]

A companion phase III study was conducted in 179 patients in England in patients with standard risk medulloblastoma using the same pre-RT CHT followed by CSRT compared to CSRT alone. A benefit to multi-modality therapy was observed. The 5 year PFS in the multi-modality arm was 74% compared to 59.8% in the standard CSRT arm.[19] However, none of the studies, including our own, confirmed a significant prolongation of survival related to either an objective response to pre-RT CHT or the use of pre-RT CHT.

The standard radiotherapy technique for PNET employs a daily fraction size of 1.8 Gy with a cumulative craniospinal dose of 36 Gy and a primary tumor dose of 54 Gy. Historical data confirms that the primary tumor dose should be at least 50 Gy but the optimum upper limit has not been clearly defined. [8] Although 36 Gy is considered the standard dose for high risk patients, the safe and effective dose for standard risk patients is lower (24 Gy) if adjuvant CHT. is used.[1] [2]

Hyperfractionation consists of dividing the daily dose into several smaller components usually separated by 6–8 hours. The time interval selected is a function of normal tissue repair kinetics. The intent is to have 4 to 5 half-lives of repair completed before the next fraction, thereby limiting cumulative toxicity to normal tissues. In several model systems the repair half-life of normal tissue is 1.5–2 hours, compared to a much longer duration in tumors.[20] Hyperfractionation typically employs smaller doses than conventional fractionation (1.8–2.0 Gy). Late normal tissue injury is exquisitely sensitive to fraction size, whereas radiosensitive tumors have either no or very small shoulders on their survival curves. This implies that smaller

fraction size would be more sparing of normal tissue yet kill tumors efficiently. [21] Collectively, this effect of reducing fraction size and increasing total cumulative dose is theoretically equitoxic to normal tissue compared to a single daily fraction, and results in escalation of the tumoricidal biological total dose. Several pilot studies have reported preliminary results of both efficacy and late effects in children with standard risk medulloblastoma.[9,10,22]

In a pilot study conducted at NYU Medical Center, hyperfractionated CSRT (1 Gy BID) was administered to a total cumulative dose of 72 Gy to the primary tumor and 36 Gy to the craniospinal axis in 15 standard risk patients and 40 Gy CSRT to 8 high risk medulloblastoma/PNET patients. All 23 medulloblastoma patients received the same adjuvant chemotherapy for 9 months. CSRT was well tolerated by all patients without significant treatment delays but 2 patients could not complete adjuvant chemotherapy because of excessive hematological toxicity. Only 1 of 15 patients with standard risk disease relapsed after 5 years and the 5 year PFS exceeded 90%. There was a very limited and less favorable experience in 4 patients with high M stages and 4 other PNET with non-cerebellar primary tumors.[9] CCG 9931 used a similar RT dose and schedule for the high risk patients but CHT was given prior to rather than following CSRT.

The feasibility of CCG 9931 therapy was acceptable according to protocol guidelines and was similar to that reported in other large clinical medulloblastoma trials of pre-RT CHT. Overall, 85 of 124 (69%) patients completed 5 courses of CHT and RT in a median of 6.1 months, which was well within the protocol limits of 9 months. The supportive care measures including the use of G-CSF, platelet transfusions and parenteral alimentation facilitated the timely completion of therapy. Treatment delays in the completion of RT was documented in 32% of patients compared to 30% in the German HIT ’91 study.[18] Although no unexpected acute toxicities were encountered during the CCG 9931 radiation experience, the twice daily RT treatment schedule did impact on quality of life. Patients who required conscious sedation remained NPO for most of the day. Their nutritional status would have been compromised if nutritional supplements were not provided.

Several observations, both pre-clinical and clinical, suggest that hyperfractionated RT schedules spares RT-induced late effects. The neuroendocrine clinical data are most convincing and the thyroid gland, located at the junction of the overlapping cranial and spinal fields and in close proximity to the spinal cord is a sensitive indicator of late radiation damage. Several studies have documented a lower incidence of primary hypothyroidism after > 5 years follow-up, e. g., 62% after standard CSRT vs. 14% after hyperfractionated CSRT. [23], [24] The use of proton beam offers similar organ sparing benefits. [25,26].

In conclusion, CCG 9931 represents one of the largest (124 patients) phase II studies of completely staged, high risk medulloblastoma/PNET patients. It validated the feasibility of a treatment paradigm consisting of prolonged pre-RT CHT followed by hyperfractionated RT. Pre-RT CHT did not have a significant impact on survival, possibly due to its long duration of 5 months. The phase II design prohibits survival comparisons with other studies. A randomized phase III design comparing standard vs. hyperfractionated CSRT would be required to determine relative differences in survival and late effects in this high risk population.

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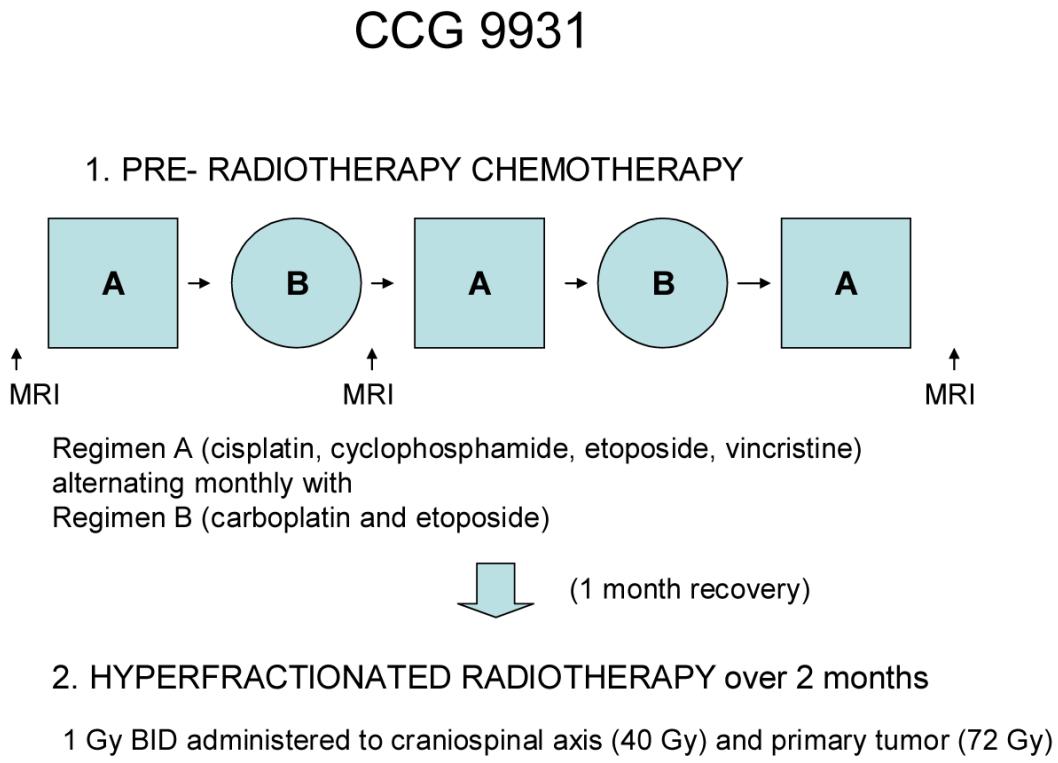

Figure 1.
Protocol Schema

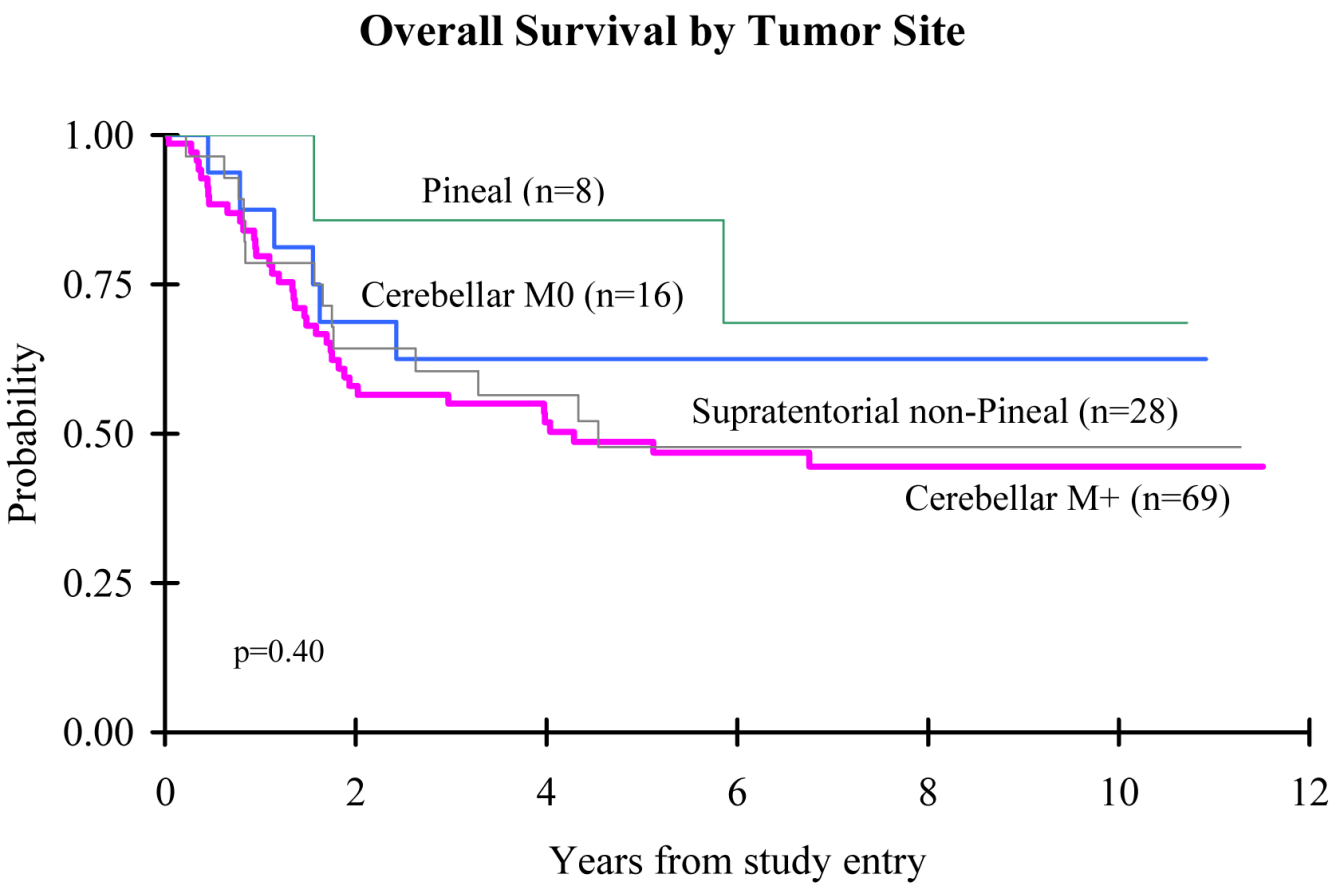

Figure 2.
Overall survival by tumor site

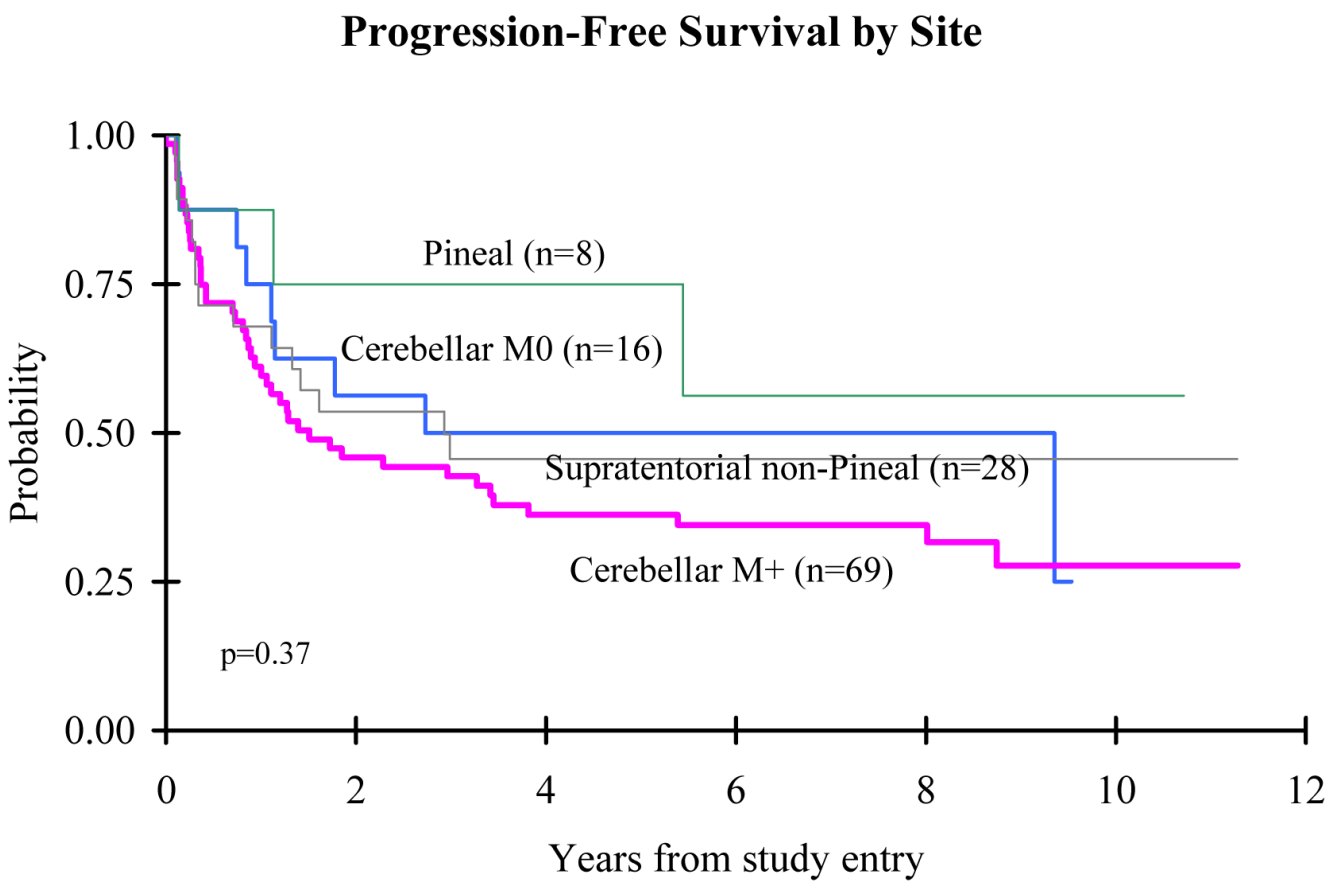

Figure 3.
Progression-free survival by tumor site

Table 1

Patient Selection by M-Stage, Site and Post –op Residual

M-Stage	Cerebellar	Non-Cerebellar	Total
M1–3	69	6	75
M0, ≥ 1.5 cm^2	16	15	31
M0, < 1.5 cm^2	0	18	18
Total	85	39	124

Table 2

5 year PFS and OS by Tumor Site, M stage and Post-op Residual Tumor

Site	N (121)	PFS	OS
Cerebellar – M0, > 1.5 cm^2	16	50 ± 13	63 ± 12
Cerebellar - M+	69	36 ± 6	49 ± 6
Supratentorial - non Pineal	28	46 ± 10	48 ± 10
Pineal	8	75 ± 15	86 ± 13