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Prognostic Value of Medulloblastoma Extent of Resection After Accounting for Molecular Subgroup: An Integrated Clinical and Molecular Analysis

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Summary

Background—Incomplete surgical resection of medulloblastoma is controversially considered a marker of high-risk disease; driving aggressive surgical resections, “second-look” surgeries, and/or intensified chemoradiotherapy. All prior publications evaluating the clinical importance of extent of resection (EOR) failed to account for molecular subgroup. We analysed the prognostic value of EOR across 787 medulloblastoma samples in a subgroup-specific manner.

Methods—We retrospectively identified patients from Medulloblastoma Advanced Genomics International Consortium (MAGIC) centres with a histological diagnosis of medulloblastoma and complete extent of resection and survival data. Specimens were collected from 35 international institutions. Medulloblastoma subgroup affiliation was determined using nanoString gene expression profiling on frozen or formalin-fixed paraffin-embedded tissues. Extent of resection (EOR) based on post-operative imaging was classified as gross total (GTR), near total (NTR, $<1{\cdot}5cm^2$), or subtotal (STR, $\geq 1{\cdot}5cm^2$). Overall survival (OS) and progression-free survival (PFS) multivariable analyses including subgroup, age, metastatic status, geographical location of therapy

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Ethics Committee Statement

All samples were collected and processed in accordance with the Ethics Review Board of the Hospital for Sick Children and collaborating institutions.

Contributors

EMT, TH, VR, EB, and MDT designed the study. MDT procured financial support. EMT, VR, MR, BL, SKK, JYL, ANR, CG, KKL, HKN, TK, WAG, MPP, SP, YJC, JM, IFP, RH, SL, WI, ARH, AJ, MFM, AV, CFC, TS, NK, NH, NJ, TG, MG, KZ, JS, LK, AK, LB, PH, US, SJ, PJF, JMK, MLV, DDB, SG, REM, ESL, LM, JRL, JBR, RV, MKC, RCT, LC, CCF, JP, XF, KMM, PAN, MK, DTJ, ELA, DJS, JAC, AN, EGM, JJO, AJ, NG, WAW, DJM, CEH, UT, AK, SMP, RJP, and MDT collected data. VR, SKK, JYL, ANR, CG, KKL, HKN, TK, WAG, MPP, SP, YJC, JM, IFP, RH, SL, WI, ARH, AJ, MFM, AV, CFC, TS, NK, NH, NJ, TG, MG, KZ, JS, LK, AK, LB, PH, US, SJ, PJF, JMK, MLV, DDB, SG, REM, ESL, LM, JRL, JBR, RV, MKC, RCT, CCF, JP, XF, KMM, PAN, MK, DTJ, ELA, JAC, AN, EGM, JJO, NG, WAW, DJM, CEH, UT, AK, PD, JTR AK, SMP, RJP, and MDT provided materials. All authors analysed and interpreted the data. TH performed the statistical analyses. EMT, TH, VR, EB, MR, DDB, PD, AK, RJP, and MDT wrote the manuscript. All authors approved the final report.

Declaration of Interests

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(North America/Australia vs world), and adjuvant therapy regimen were performed. The primary endpoint was the impact of surgical EOR by molecular subgroup and other clinical variables on OS and PFS.

Findings—787 medulloblastoma patients (86 WNT, 242 SHH, 163 Group 3, and 296 Group 4) were included in a multivariable Cox model of PFS and OS. The marked benefit of EOR in the overall cohort was greatly attenuated after including molecular subgroup in the multivariable analysis. There was an observed PFS benefit of GTR over STR (hazard ration [HR] 1·45, 95% CI; 1·07–1·96, p=0·02) but there was no observed PFS or OS benefit of GTR over NTR (HR 1·05, 0·71–1·53, p=0·82 and HR 1·14, 0·75–1·72, p=0.55). There was no statistically significant survival benefit to greater EOR for patients with WNT, SHH, or Group 3 patients (HR 1·03, 0·67–1·58, p=0·9 for STR vs. GTR). There was a PFS benefit for GTR over STR in patients with Group 4 medulloblastoma (HR1·97, 1·22–3·17, p=0·01), particularly those with metastatic disease (HR 2·22, 1–4·93, p=0·05). A nomogram based on this multivariable cox proportional hazards model shows the comparably smaller impact of EOR on relative risk for PFS and OS than subgroup affiliation, metastatic status, radiation dose, and adjuvant chemotherapy.

Interpretation—The prognostic benefit of EOR for patients with medulloblastoma is attenuated after accounting for molecular subgroup affiliation. Although maximal safe surgical resection should remain the standard of care, surgical removal of small residual portions of medulloblastoma is not recommended when the likelihood of neurological morbidity is high as there is no definitive benefit to GTR over NTR. Our results suggest a re-evaluation of the long-term implications of intensified craniospinal irradiation (36 Gy) in children with small residual portions of medulloblastoma.

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Introduction

Current clinical risk stratification of medulloblastoma patients separates children into average risk and high-risk strata. High-risk disease is defined by the presence of metastases at diagnosis, age < 3 years, and/or residual disease ≥ 1·5 cm^2.[2.1–5] The published literature is controversial on the prognostic benefit of gross total resection (GTR) versus subtotal resection (STR) or biopsy (see appendix p. 44).[1,2,6–14] Currently, many patients with ≥ 1·5 cm^2 of residual disease are either subjected to second look surgery to achieve a GTR, or treated with high-risk protocols including higher doses of craniospinal irradiation and more intensive chemotherapy.[2,15]

Aggressive resection of medulloblastoma may be associated with increased surgical complications. Post-surgical neurologic morbidity for children with medulloblastoma regardless of extent of residual tumour is 24% and increases as high as 44% after GTR.[16,17] The incidence of posterior fossa syndrome/cerebellar mutism may be increased after GTR as compared to less complete resections.[18] The majority of patients with postoperative cerebellar mutism syndrome have mild to severe persistent cognitive deficits, speech deficits, and ataxia.[19,20] Many medulloblastomas have an attachment to the floor of the fourth

ventricle; removal of small medulloblastoma residua adherent to critical structures (i.e., brainstem) can greatly increase morbidity.[21,22] Determining the appropriate balance between extent of resection and respect for critical structures while optimizing prognosis is an unresolved question in neurosurgery and neuro-oncology.

Medulloblastoma is no longer considered a single entity, but rather comprises four distinct molecular subgroups (WNT, SHH, Group 3, Group 4) with distinct demographics, clinical features including prognosis, transcriptomes and genetics.[4,23–31] Critically, all prior publications on the prognostic importance of EOR for medulloblastoma were done without knowledge of subgroup affiliation (see appendix p. 44).

Methods

Specimen Processing and Subgroup Determination

Surgical resections took place from April 1997 to February 2013 and specimens were sterilely stored at each institution. Samples were collected and processed in accordance with the Ethics Review Board of the Hospital for Sick Children and our 35 collaborating institutions. Each centre provided information and specimens for one to 139 patients. The largest 10 centres provided 505/787 (64%) of the data. Between one and six different surgeons from each institution performed tumour resections. Extrapolating from the experience at the Hospital for Sick Children which has one of the highest surgical volumes in North America, each individual surgeon would have operated on less than 20 patients each. Therefore, adjusting for “surgeon” in the multivariable analysis was not feasible, particularly for institutions contributing small numbers. Although there is a small overlap with a previously published report from our group with respect to overall survival and cytogenetics, there is no known overlap of cases ascertained in this series with any previously published cohorts from our group or any cooperative cohort with respect to surgical and oncological treatment, with the exception of a recently published institutional cohort from the Hospital for Sick Children.[32] Subgroup affiliation was determined using nanoString limited gene expression profiling on specimens weeks to years after surgical resection.[33,34]

Determination of Extent of Resection

Extent of resection was based on surgeons reports and confirmed on post-operative gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI), or less commonly contrast-enhanced computed tomography (CT) by each contributing institution. The non-centralized radiographic review was blinded to molecular subgroup. Based on post-operative imaging, no residual tumour was defined as GTR, $< 1{\cdot}5\ cm^2$ residual tumour was defined as near total resection (NTR), and $\geq 1{\cdot}5\ cm^2$ residual tumour was defined as STR.[1,2]

Statistical Analysis

Association between EOR and clinico-pathological variables was tested with Fisher s exact test. Log-rank test was used to compare groups in terms of survival. Univariate and multivariable Cox proportional hazard regression was used to estimate hazard ratios including 95% confidence intervals. Six hundred twenty-eight of 778 (81%) of the patients

had complete data for all covariables used in multivariable Cox regression. For all multivariable Cox regression models, missing data in covariables were accounted for using multiple imputations. Predictive mean matching based on 50 bootstrap samples with 5 burn-in iterations was used to perform imputations. This approach works for continuous, binary, and categorical predictors. Briefly, in each bootstrap sample, missing data for each variable is predicted conditioned on all other variables. For each imputed data set, a multivariable Cox regression model is fitted. Estimates from all imputed data sets are then combined in a weighted approach to get final Cox regression model estimates. Imputations were carried out with R package Hmisc function aregImpute.[35] Nomograms of multivariable models were generated with R package rms. Forest plots were used to display hazard ratios of EOR in subgroups. To account for adjuvant chemotherapy and radiation differences, tests on difference in survival were stratified or adjusted for location, North America/Australia (Children s Oncology Group members) versus others primarily due to the uniformity of risk-adapted therapy from COG affiliated centres compared to more heterogeneous treatment across the remaining worldwide centres. Chemotherapy and radiation at diagnosis were analysed, however, treatment regimen at recurrence was not analysed given the low percentage of patients that progressed and the heterogeneity of salvage therapy amongst the 35 collaborating institutions. Metastatic status was analyzed as the presence (M+) or the absence (M0) of metastases at diagnosis to simplify the multivariable analysis, particularly given that patients were divided into 4 different molecular subgroups. This is consistent with another recent publication accounting for medulloblastoma subgroup.[36] We used interaction tests in Cox regression to formally assess heterogeneity of EOR effect between subgroups. The quantitative covariate, age, was assessed for non-linear functional relationship using martingale residuals without indication of a violation. We then determined that multivariable fractional polynomials or restricted cubic splines would not improve the fit of age in the model. All tests were two-sided. P-values below 0·05 were considered statistically significant. Survival analysis was performed using the R-package survival (v2.37) and ggplot2 (v0.9.3.1). All analyses were performed in the R statistical environment (v3.1.3).

Role of Funding Sources

No funding source had a role in the study design; data collection, analysis, or interpretation; or writing of the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication

Results

Patients

A cohort of 787 patients was analysed (Table 1, see appendix p. 21). Complete EOR data was available and analysed in 787 patients, gender in 765 patients, age in 771 patients, radiation in 718 patients, craniospinal radiation dose in 690 patients, chemotherapy in 738, metastatic status in 735, and geographic region/COG status in all patients (Table 1). Patients were deemed ineligible for study inclusion if they had incomplete molecular subgroup, extent of resection, or survival data. There were 86 WNT, 242 SHH, 163 Group 3, and 296 Group 4 patients. There were 159 STR, 109 NTR, and 519 GTRs. No statistically significant difference in distribution of GTR, NTR, and STR were observed between the four subgroups

(p=0·08). For PFS analysis, there were 251 events in 738 patients. For OS analysis, there were 201 events in 778 patients. Patients with incomplete survival data originated from 14 different centres and there was no pattern of missingness. Three hundred and eleven of 577 patients (54%) without an event (death) had 5 year follow-up while 413/577 (72%) had 3 year follow-up (interquartile range 31.9–60 months). Two hundred sixty-three of 487 patients (54%) without an event (progression) had 5 year follow-up while 347/487 (71%) had 3 year follow-up (interquartile range 32–60 months). The mean follow up for event-free patients was 71.9 months (95% CI 67·3–76·5). To compare our cohort to the published literature, we evaluated the prognostic value of EOR without accounting for subgroup, replicating prior results showing a benefit for increased EOR (STR vs. GTR): PFS (HR 1.8, 1·3–2·4, p<0·0001) and OS (HR 1.6, 1·2–2·2, p=0·01) (Fig. 1).[1,2,8] We conclude that our cohort is similar to previously published cohorts. Similar to prior publications detailing subgroups, WNT patients had the best PFS and OS (Fig. 1), followed by Group 4 and SHH, then Group 3.[23,30,37]

Subgroup-Specific Analysis of Survival

A univariate analysis of PFS and OS by EOR was then performed in a subgroup-specific manner (Fig. 2). Notably, no significant interaction between subgroup and EOR was observed, indicating that the EOR effect is not significantly different between the subgroups (see appendix p. 1).

We subsequently performed a multivariable analysis of PFS and OS in a subgroup-specific manner. In patients with WNT tumours, the increase in risk of progression associated with STR (HR 3·04, 0·4–23·3, p=0·28) and NTR (HR 1·91, 0·39–9·35, p=0·43) did not reach statistical significance (see appendix p. 1). Overall survival risk with STR (HR 2·4, 0·26–22·09, p=0·44) but not NTR (HR 0·9, 0·12–6·88, p=0·92), also did not reach statistical significance (see appendix p. 2). The implications of EOR for WNT patients are somewhat limited by the small cohort with only 14 STRs and 21 NTRs (Fig. 2).

In a multivariable analysis of SHH patients, only M status and craniospinal radiation were significantly associated with progression. Neither STR (HR 1·04, 0.6–1.81, p=0·88) nor NTR (HR 0·82, 0·35–1·92, p=0·65) were associated with an increased risk of progression in SHH patients (see appendix p. 3). Similarly, for OS, only M status was significant, as neither STR (HR 1·06, 0·57–1·96, p=0·85) nor NTR (HR 0·78, 0·31–1·95, p=0·56) were associated with a shortened survival (see appendix p. 4). In a univariate analysis, when SHH patients were stratified into M0 and M+, we observed no statistically significant difference in survival with an STR (see appendix p. 48).

For patients with Group 3 tumours, variables associated with progression risk included M status and craniospinal radiation. Neither STR (HR 1·20, 0·64–2·27, p=0·57) nor NTR (0·61, 0·27–1·4, p=0·25) were significantly associated with progression for Group 3 patients (see appendix p. 5). Variables associated with risk of death included M status, age, and chemotherapy. No increased risk of death due to STR (HR 0·84, 0·44–1·61, p=0·60) or NTR (HR 0·81, 0·38–1·73, p=0·59) was observed (see appendix p. 6).

For patients with Group 4 tumours, variables associated with progression risk included STR (HR 1·97, 1·22–3·17, p=0·01), craniospinal radiation, and geographic treatment location, while NTR was not significant (HR 1·24, 0·7–2·2, p=0·45) (see appendix p. 7). Only lack of craniospinal radiation and geographic location of treatment (North America/Australia vs Europe/Asia) were associated with increased risk of progression. Similar but not statistically significant OS results were observed for STR (HR 1·67, 0·93–2·99, p=0·08) and NTR (HR 1·38, 0·71–2·71, p=0·34) (see appendix p. 8). However, the adverse effect on survival of an STR in Group 4 was largely restricted to patients with metastatic disease (see appendix p. 8–10, 49). Specifically, in a multivariable model using age, craniospinal radiation and site of treatment, the observed non-statistically-significant beneficial effects of increased EOR on PFS and OS are largely limited to M+ patients: PFS M0 patients (HR 1·36, 0·67–2·75, p=0·39), PFS M+ patients (HR 2·22, 1–4·93, p=0·05); OS M0 patients (HR 1·29, 0·52–3·17, p=0·59), OS M+ patients (HR 2·09, 0·79–5·59, p=0·14).

Analysis of Survival Based on Metastatic Status and Age

Multivariable analyses were then performed in a metastatic and age-specific manner. In M0 patients, variables associated with progression risk included geographic location of treatment, subgroup, and craniospinal radiation. Neither NTR (HR 0·94, 0·55–1·64, p=0·82) nor STR (HR 1·15, 0·72–1·82, p=0·56) (see appendix p. 13) were associated with a higher progression risk. Variables associated with risk of death included geographic treatment location, subgroup, and craniospinal radiation. Neither NTR (HR 0·84, 0·41–1·7, p=0·62) nor STR (HR 1·03, 0·59–1·77, p=0·93) were associated with an OS risk (see appendix p. 14). In summary, no increase in risk with NTR was observed (HR < 1) and the observed increase in risk with STR was minimal.

In M+ patients, variables associated with progression risk included subgroup, craniospinal radiation, and geographic treatment location. Neither NTR (HR 1·09, 0·6–1·97, p=0·78) nor STR were associated with increased PFS (HR 1·53, 0·98–2·41, p=0·06) (see appendix p. 15). Variables associated with risk of death included subgroup, chemotherapy, and geographic treatment location. Neither NTR (HR 1·13, 0·63–2·04, p=0·68) nor STR (HR 1·33, 0·82–2·16, p=0·25) were associated with an increase of death (see appendix p. 16).

There was a significant interaction between age and EOR (p=0·03 for PFS, p=0·01 for OS), indicating a different prognostic impact of STR in both age groups. In patients < age 3, variables associated with progression risk included subgroup, while NTR (HR 0·47, 0·19–1·17, p=0·11) and STR (HR 0·73, 0·35–1·51, p=0·39) did not have an association with increased risk (see appendix p. 17). Similar to PFS risk models, neither NTR (HR 0·56, 0·22–1·4, p=0·21) nor STR (HR 0·44, 0·18–1·06, p=0·07) were associated with increased risk of death (see appendix p. 18). Rather, we observed a decreased risk of death with STR. In summary, GTR did not confer a PFS or OS benefit.

Multivariable Analysis of Survival and Direct Comparison by Extent of Resection

Multivariable analysis demonstrated STR, subgroup, M+ status, craniospinal radiation, and geographic location as significant predictors of PFS (Table 2). Near total resection had no increased risk of progression (HR 1·05, 0·71–1·53, p=0·82). Multivariable analysis of OS

identified significant associations with subgroup, M+ status, craniospinal radiation, and geographic location (Table 3). Nomograms of the multivariable model were prepared to graphically illustrate the relative clinical impact of each variable to predict 3 and 5 year PFS and OS (Fig. 3).

Multivariable direct comparisons of GTR, NTR, and STR were performed for both PFS and OS for the entire cohort, and within each subgroup (Fig. 4). No subgroups were identified with a significantly increased the risk of progression when comparing NTR vs. GTR. STR showed a consistent trend towards a worse outcome than NTR across all subgroups. For STR vs. GTR, we found that STR portends a modest progression risk compared to GTR for the entire cohort, Group 4 patients, and patients ≥ age 3 (Fig. 4). The metastatic Group 4 patients likely drive age related effects, as there is no observable effect for WNT, SHH, or Group 3 patients. The same analysis for overall survival does not show a difference between STR and GTR for Group 4 patients (Fig. 4). Unexpectedly, for patients < age 3, GTR and NTR do not improve survival (Figure 4). Univariate analysis and multivariable analysis adjusted only for chemotherapy and radiotherapy regimens, yielded similar results (see appendix p. 51). A sensitivity analysis of random effects and institution demonstrated similar results with and without accounting for institution (see appendix p. 43).

Discussion

Our main findings are that the value of increased extent of resection is largely attenuated after accounting for molecular subgroup, that NTR appears to be prognostically equivalent to GTR, and that the magnitude of the beneficial clinical effect on prognosis of a GTR is smaller than other known medulloblastoma risk factors. To our knowledge, this study evaluates the largest cohort of patients to date on the role of extent of resection in the treatment of medulloblastoma.

Clinical Importance of Extent of Resection

Currently, the goal of surgical resection upfront for medulloblastoma patients is a safe GTR without significant neurological sequelae. If there is tumour adherent to critical structures, the goal is to leave a residual < 1·5 cm^2, a NTR.[21] There is a controversial perception in the neurosurgical community that a GTR is prognostically superior to an NTR. Findings in the current manuscript highlight the lack of prognostic difference between GTR and NTR and should convince surgeons to minimize morbidity when removing small residual portions of tumours adherent to critical structures. STR can range from just larger than 1·5 cm^2 up to small limited biopsies. This value of < 1·5 cm^2 was based largely on postoperative CT scans[1,2] with limited resolution compared to modern MR imaging. This was established as part of CCG921, which ran in the late 1980 s where treatment and outcomes were significantly different when compared to current cisplatin-based therapy, and during which the histological classification likely included other entities such as atypical teratoid rhabdoid tumors. Furthermore, approximately 50% of medulloblastomas (mostly Group 4) do not enhance or have heterogeneous enhancement.[38] Nonenhancing residual tumor can easily be missed even on modern postoperative MRI, particularly when located between the cerebellum and brainstem. A large prospective radiographic study using modern 3D MRI

volumetrics with a receiver operating curve is needed to determine exactly how much residual tumour is truly predictive of a poor prognosis.

There are a number of reasons why our data showing a lack of definitive association between EOR and survival is not surprising. Review of the literature revealed a roughly equal number of publications that did, and did not find an association between increased EOR and OS (see appendix p. 44). Despite clinical equipoise that is arguably justified by the existing literature, most neurosurgeons attempt a maximal safe gross total resection in attempt to maximize PFS and OS in the absence of more definitive data.

Prior prospective clinical trials have cast doubt on the role of extent of resection for children with medulloblastoma. Packer and colleagues found a 5-year event-free survival of 83% ± 2·2% in M0 patients with < 1·5cm^2 residual tumour (n = 313) compared to 75% ± 13% in M0 patients with ≥ 1·5 cm^2 (n = 15) despite both groups having received only 23·4 Gy of craniospinal irradiation.[5] Gajjar and colleagues found zero of six patients with residual tumour > 1·5 cm^2 treated as “high-risk” in the St. Jude Medulloblastoma-96 protocol had evidence of disease with a median follow up of over 8 years.[3] The HIT2000 multicentre clinical trial cohort did not demonstrate an association of residual tumour > 1·5 cm^2 and event-free survival.[36] The SIOP PNET4 study, which did not include subgroup information, enrolled non-metastatic, subtotally resected tumours as average risk disease, and did find subtotal resection was the strongest negative prognostic factor, however this was limited by only 31 of 340 patients having a residual ≥ 1·5cm^2.[39] Finally, we recently reported that in patients with Group 3 and 4 medulloblastoma, the site of recurrence is almost invariably metastatic and not the local tumour bed.[34] In Group 4 patients, the benefit of a subtotal resection appeared to be largely restricted to metastatic patients, rather than non-metastatic patients who currently receive intensified craniospinal irradiation when residual disease exceeds 1·5cm^2. It is unclear why metastatic Group 4 patients appear to have a poorer survival with a STR, but the simplest proximate explanation is the degree of metastatic dissemination is higher in this group, hence there is a reduced impetus for the surgeon to pursue an aggressive resection. In the STR group, the average residual tumour size may also be larger for M+ patients than M0 patients.

We would like to emphasize that all patients benefit from generous tumour debulking, and decompression of the brainstem. Resection of the bulky, dorsal portion of the tumour is usually very safe and seldom a cause of morbidity. Our findings do not address or endorse a strategy in which only a small diagnostic biopsy is done followed by adjuvant therapy, as this type of patient is seldom seen, and was not included in the current data set. Clinical actionability of the current manuscript can be limited at presentation as the subgroup of the patient s tumour is usually not known definitively at the time of surgery. However, our findings could certainly inform the value of second look surgery for small residual tumours.

Adjuvant Therapy Implications

At many institutions worldwide, patients are considered “high risk” if there is ≥ 1·5 cm^2 residual tumour on postoperative MRI. This has profound implications regarding the amount of adjuvant craniospinal radiation these patients receive (36 Gy compared to 23 Gy for “average risk” patients at most COG and International Society of Paediatric Oncology-

associated centres). Notably, patients from North America/Australia COG centres in this study had significantly better PFS and OS than non-COG centres, possibly due to the relatively uniform adjuvant CSI protocols and heterogeneous treatment in the global cohort. There is clear and well demonstrated decrease in long-term IQ and quality of life in patients who receive high dose, as compared to low dose craniospinal irradiation.[40] In the current study, we could not find a definitive association between increased EOR and PFS or OS in patients with WNT, SHH, and Group 3 medulloblastoma. A minor subset of SHH group tumours demonstrate extensive nodular histology (MBEN)[24] which has been shown to have the most favourable prognosis of all histological types[7] and is typically found in infants.[41] Garre et al determined that residual tumour ≥ 1·5 cm^2 was not significantly associated with OS in patients with huge MBEN tumours due to familial tumor predisposition syndromes.[41] In Group 4 medulloblastoma patients, and patients ≥ age 3, there may be a role for more aggressive resections to achieve residual disease of under 1·5cm^2, although the relative benefit on overall survival is indeterminate and has to be weighed against the risks of aggressive surgical resections. Clinicians may need to weigh the modest risk of residual disease on survival as compared to the marked risk of poor long-term quality of life when deciding whether or not to treat M0 patients with residual disease with high dose craniospinal radiotherapy.

Limitations of this work include the lack of a central radiographic review and its retrospective nature. Discrepancies in central and institutional radiographic review of residual medulloblastoma can occur as can poor quality postoperative imaging.[5] A prospective trial randomizing patients to < 1·5 cm^2 residual vs. aggressive debulking but ≥ 1·5 cm^2 residual, while accounting for molecular subgroup would be the gold standard to determine the role of subtotal resection. Clearly, this would be both ethically and practically impossible to achieve. Assuming survival rates as observed in our cohort (GTR patients have 83% (95% CI 79%–87%) survival after 3 years) and based on the hazard ratio from the multivariable analysis, in a trial with 3 years recruitment and 3 years minimal follow-up, one-sided α 2.5, 0.2, and clinical acceptable non-inferiority margin of 1.2 for the hazard ratio for the upper confidence limit, more than 6,400 patients would be required for such a trial. Indeed, the current manuscript contains 787 medulloblastoma patients, to our knowledge, the largest cohort to date in which the value of EOR has been assessed, and contains the largest number of incompletely resected medulloblastomas analysed to date. While we are unable to definitively exclude a small, statistically significant benefit for GTR, the authors would point out that the benefit of EOR has never been definitively demonstrated in a proper randomized trial, and that if the current data for EOR were instead for a novel drug or therapy, that this novel therapy would be rejected out of hand even if it had minimal side effects. Additionally, any potential age-related differences in clinical importance of extent of resection require further evidence in a prospective randomized trial.

We conclude that while the initial surgical goal should be GTR, there is no prognostic difference between NTR and GTR, therefore, GTR should not be pursued over NTR if there is clinical risk of neurological sequelae. The role of EOR in medulloblastoma is controversial in the literature, and we observe no profound clinical benefit on survival for increased EOR in WNT, SHH, Group3, or M0 Group 4 patients. While we cannot rule out any significant benefit due to EOR due to insufficient sample size, the clinical trial to

address this question is not feasible due to an immense sample size, and our nomogram demonstrates that the magnitude of any possible benefit is modest. These data question the clinical benefit of second look surgery for small residual medulloblastoma due to the possible morbidity of surgery and the delay in the commencement of radiation. Finally, both prior publications and the current manuscript question whether both statistical significance and the clinical magnitude of effect when using residual disease as a criteria to classify a patient as high risk and precipitate high-dose craniospinal radiotherapy. The relatively small effect size of residual disease as compared to the marked long-term neurocognitive side effects of high dose craniospinal radiotherapy suggest that the paediatric neuro-oncology community needs to revisit residual disease as a criteria for high risk stratification, particularly as more informative and robust molecular markers are described and validated.

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References

1. Albright AL, Wisoff JH, Zeltzer PM, Boyett JM, Rorke LB, Stanley P. Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group. Neurosurgery. 1996; 38(2):265–71. [PubMed: 8869053]
2. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol. 1999; 17(3):832–45. [PubMed: 10071274]
3. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol. 2006; 7(10):813–20. [PubMed: 17012043]
4. Ramaswamy V, Northcott PA, Taylor MD. FISH and chips: the recipe for improved prognostication and outcomes for children with medulloblastoma. Cancer genetics. 2011; 204(11):577–88. [PubMed: 22200083]
5. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006; 24(25):4202–8. [PubMed: 16943538]
6. Brasme JF, Grill J, Doz F, et al. Long time to diagnosis of medulloblastoma in children is not associated with decreased survival or with worse neurological outcome. PLoS One. 2012; 7(4):e33415. [PubMed: 22485143]
7. Rutkowski S, von Hoff K, Emser A, et al. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. J Clin Oncol. 2010; 28(33):4961–8. [PubMed: 20940197]
8. Packer RJ, Boyett JM, Janss AJ, et al. Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. J Clin Oncol. 2001; 19(2):480–7. [PubMed: 11208842]
9. Johnston DL, Keene D, Bartels U, et al. Medulloblastoma in children under the age of three years: a retrospective Canadian review. J Neurooncol. 2009; 94(1):51–6. [PubMed: 19184579]
10. Akyuz C, Varan A, Kupeli S, et al. Medulloblastoma in children: a 32-year experience from a single institution. J Neurooncol. 2008; 90(1):99–103. [PubMed: 18566744]
11. Evans AE, Jenkin RD, Sposto R, et al. The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg. 1990; 72(4):572–82. [PubMed: 2319316]
12. Stavrou T, Bromley CM, Nicholson HS, et al. Prognostic factors and secondary malignancies in childhood medulloblastoma. J Pediatr Hematol Oncol. 2001; 23(7):431–6. [PubMed: 11878577]
13. Grill J, Sainte-Rose C, Jouvet A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol. 2005; 6(8):573–80. [PubMed: 16054568]
14. Tait DM, Thornton-Jones H, Bloom HJ, Lemerle J, Morris-Jones P. Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). Eur J Cancer. 1990; 26(4):464–9. [PubMed: 2141512]
15. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol. 2013; 31(23):2936–41. [PubMed: 23857975]
16. Albright AL, Sposto R, Holmes E, et al. Correlation of neurosurgical subspecialization with outcomes in children with malignant brain tumors. Neurosurgery. 2000; 47(4):879–85. discussion 85–7. [PubMed: 11014428]
17. Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR. The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg. 1994; 20(1): 19–29. [PubMed: 8142278]
18. Korah MP, Esiashvili N, Mazewski CM, et al. Incidence, risks, and sequelae of posterior fossa syndrome in pediatric medulloblastoma. Int J Radiat Oncol Biol Phys. 2010; 77(1):106–12. [PubMed: 19695790]

19. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg. 2006; 105(6 Suppl):444–51. [PubMed: 17184075]
20. Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain : a journal of neurology. 2000; 123(Pt 5):1041–50. [PubMed: 10775548]
21. Gajjar A, Sanford RA, Bhargava R, et al. Medulloblastoma with brain stem involvement: the impact of gross total resection on outcome. Pediatr Neurosurg. 1996; 25(4):182–7. [PubMed: 9293545]
22. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery. 1995; 37(5):885–93. [PubMed: 8559336]
23. Kool M, Korshunov A, Remke M, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta neuropathologica. 2012; 123(4):473–84. [PubMed: 22358457]
24. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta neuropathologica. 2012; 123(4):465–72. [PubMed: 22134537]
25. Thompson MC, Fuller C, Hogg TL, et al. Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol. 2006; 24(12):1924–31. [PubMed: 16567768]
26. Ramaswamy V, Remke M, Shih D, et al. Duration of the pre-diagnostic interval in medulloblastoma is subgroup dependent. Pediatric blood & cancer. 2014; 61(7):1190–4. [PubMed: 24616042]
27. Northcott PA, Jones DT, Kool M, et al. Medulloblastomics: the end of the beginning. Nature reviews Cancer. 2012; 12(12):818–34. [PubMed: 23175120]
28. Northcott PA, Dubuc AM, Pfister S, Taylor MD. Molecular subgroups of medulloblastoma. Expert review of neurotherapeutics. 2012; 12(7):871–84. [PubMed: 22853794]
29. Northcott PA, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. Nature reviews Neurology. 2012; 8(6):340–51. [PubMed: 22565209]
30. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol. 2011; 29(11):1408–14. [PubMed: 20823417]
31. Dubuc AM, Remke M, Korshunov A, et al. Aberrant patterns of H3K4 and H3K27 histone lysine methylation occur across subgroups in medulloblastoma. Acta Neuropathol. 2013; 125(3):373–84. [PubMed: 23184418]
32. Shih DJ, Northcott PA, Remke M, et al. Cytogenetic prognostication within medulloblastoma subgroups. J Clin Oncol. 2014; 32(9):886–96. [PubMed: 24493713]
33. Northcott PA, Shih DJ, Remke M, et al. Rapid, reliable, and reproducible molecular subgrouping of clinical medulloblastoma samples. Acta neuropathologica. 2012; 123(4):615–26. [PubMed: 22057785]
34. Ramaswamy V, Remke M, Bouffet E, et al. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol. 2013; 14(12):1200–7. [PubMed: 24140199]
35. Harrell, FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Germany: Springer Heidelberg; 2011.
36. Pietsch T, Schmidt R, Remke M, et al. Prognostic significance of clinical, histopathological, and molecular characteristics of medulloblastomas in the prospective HIT2000 multicenter clinical trial cohort. Acta neuropathologica. 2014; 128(1):137–49. [PubMed: 24791927]
37. Ramaswamy V, Remke M, Adamski J, et al. Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients? Neuro Oncol. 2015
38. Perreault S, Ramaswamy V, Achrol AS, et al. MRI surrogates for molecular subgroups of medulloblastoma. AJNR American journal of neuroradiology. 2014; 35(7):1263–9. [PubMed: 24831600]

39. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol. 2012; 30(26):3187–93. [PubMed: 22851561]

40. Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma. J Clin Oncol. 2014

41. Garre ML, Cama A, Bagnasco F, et al. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome--a new clinical perspective. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15(7):2463–71. [PubMed: 19276247]

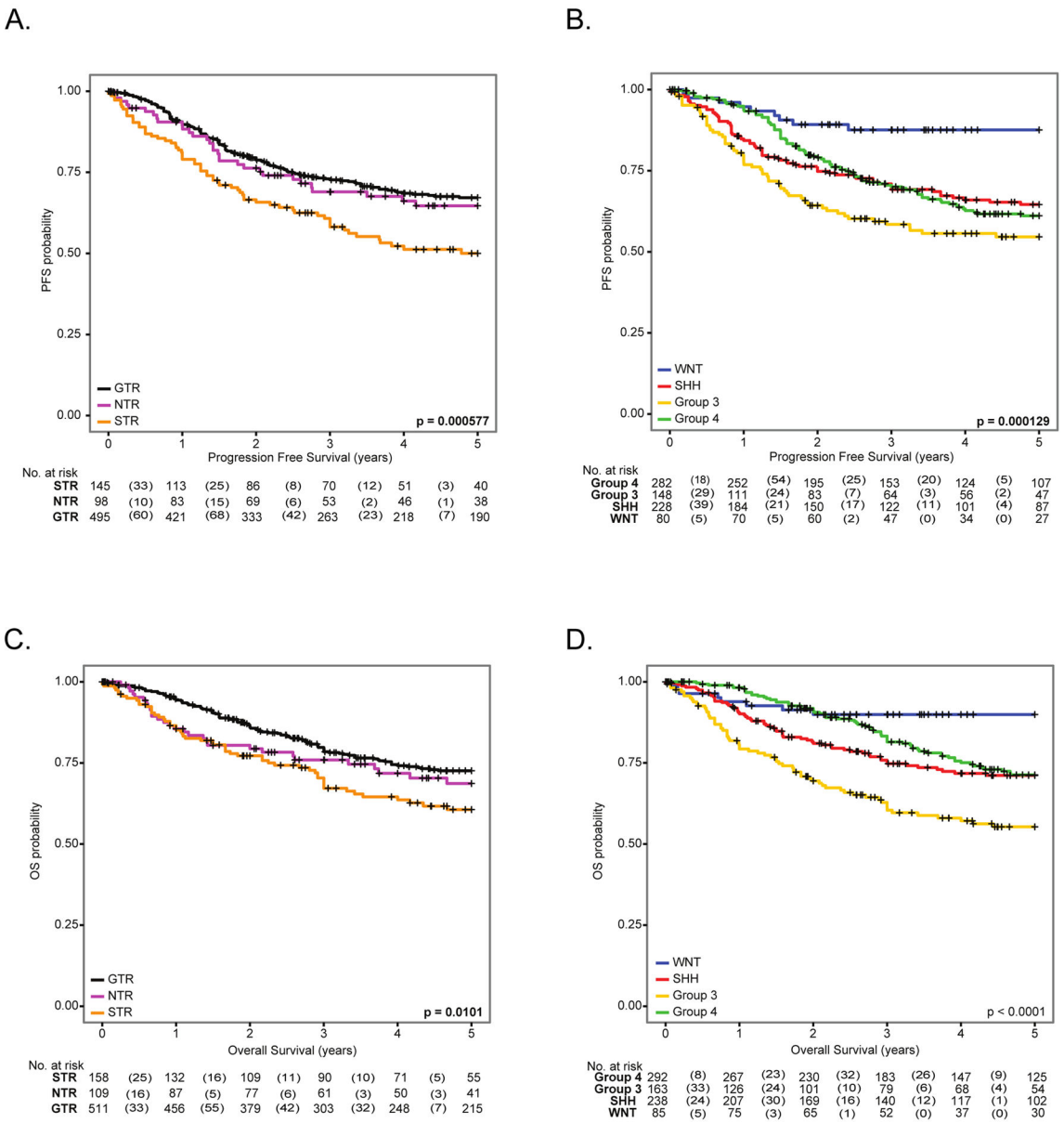

Fig 1.

Five-year PFS and OS survival curves for the entire cohort by extent of resection (A and C) and by molecular subgroup (B and D).

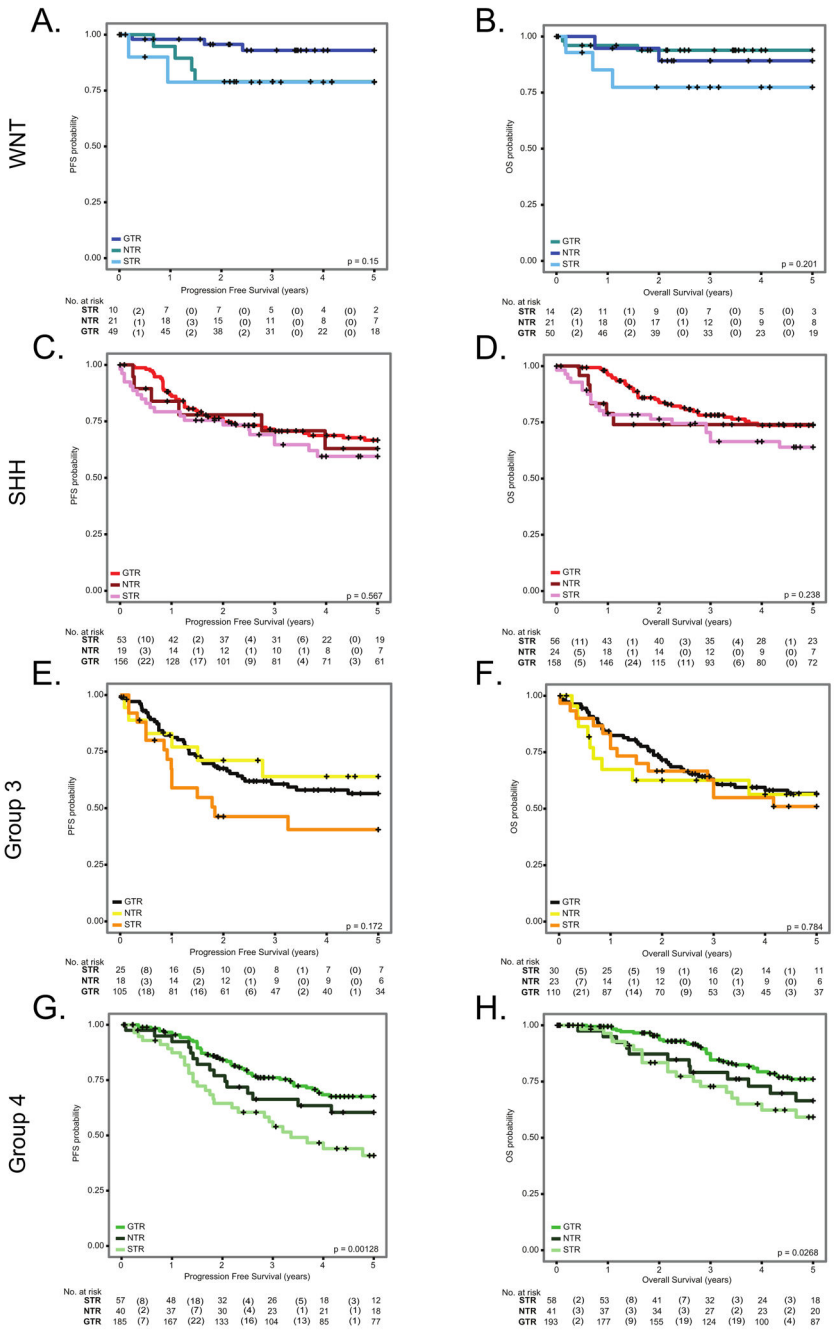

Fig 2.

Five-year PFS and OS survival curves for EOR by subgroup. There was not a significant PFS or OS advantage of those patients that had NTR or STR compared to GTR for the WNT group (A and B), the SHH group (C and D), or Group 3 (E and F). There was an association of increased EOR and both PFS and OS for Group 4 (G and H).

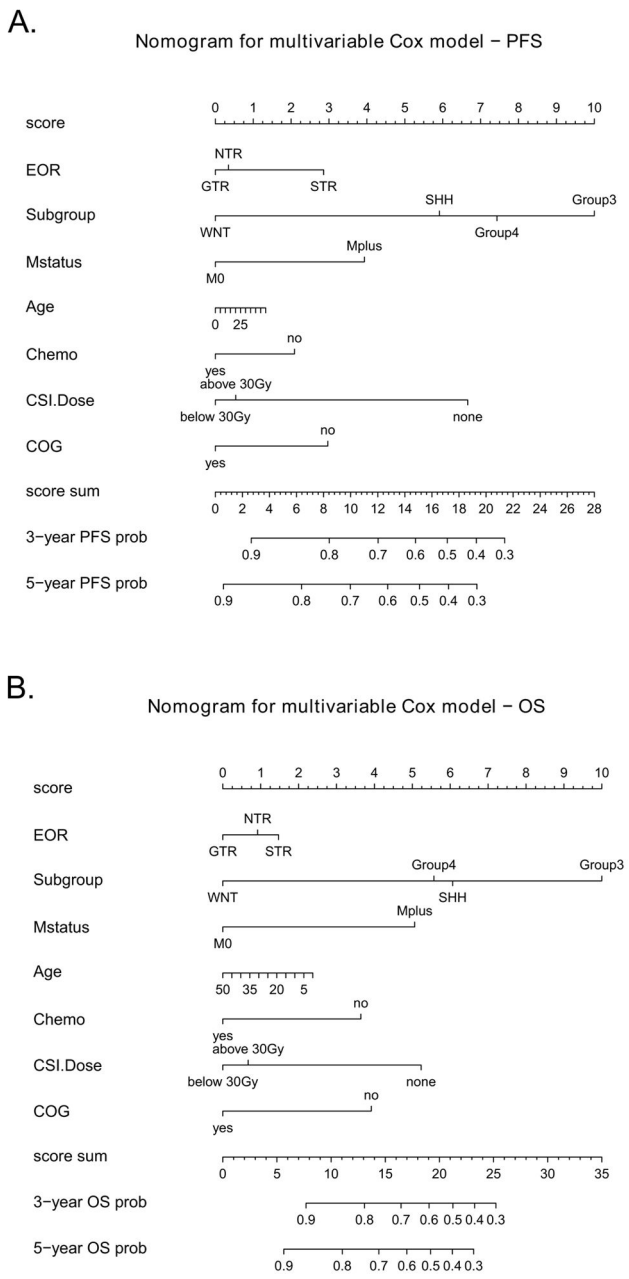

Fig 3.

Nomograms for the multivariable Cox model. The presence or absence of each variable is scored (top row). The cumulative score from each variable is used to determine 3 and 5-year PFS (A) and OS (B) probabilities.

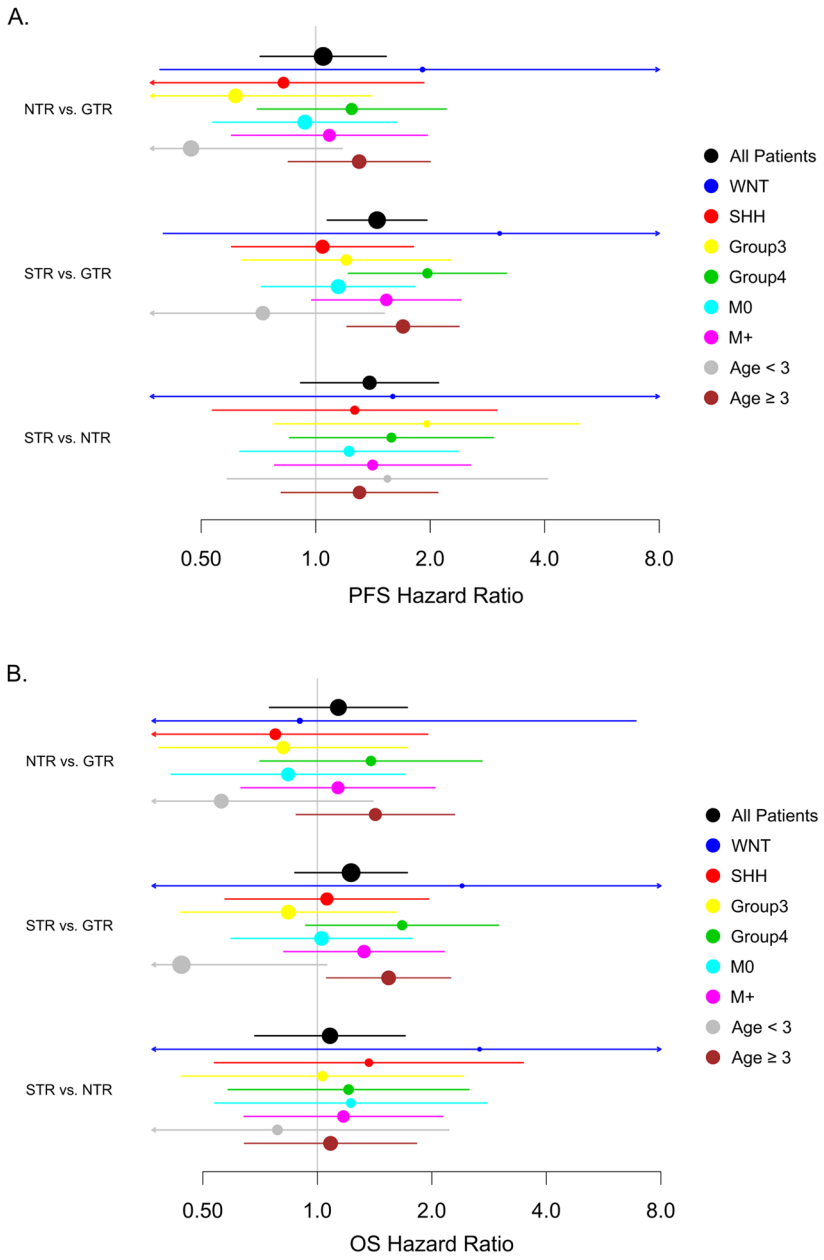

Fig 4.

Multivariable Forest Plots directly comparing EOR for PFS (A) and OS (B). Circles to the right of the grey vertical line indicate increased risk while those to the left of the grey vertical line indicated decreased risk.

Table 1

Patient Characteristics by Subgroup

Variable		WNT	%	SHH	%	Group 3	%	Group 4	%	Total	%
Extent of Resection	GTR	51	59.3	162	66.9	110	67.5	196	66.2	519	66
	NTR	21	24.4	24	9.9	23	14.1	41	13.8	109	13.8
	STR	14	16.3	56	23.1	30	18.4	59	19.9	159	20.2
p = 0.08	Total	86	100	242	100	163	100	296	100	787	100
Gender	F	49	59.8	90	38.8	41	25.8	81	27.7	261	24.1
	M	33	40.2	142	61.2	118	74.2	211	72.3	504	65.9
p < 0.0001	Total	82	100	232	100	159	100	292	100	765	100
Age	< 3	3	3.7	79	33.3	30	18.8	9	3.1	121	15.7
	≥ 3	79	96.3	158	66.7	130	81.2	283	96.9	650	84.3
p < 0.0001	Total	82	100	237	100	160	100	292	100	771	100
Radiation	No	5	6.3	68	31.5	27	18	10	3.7	110	15.3
	Yes	74	93.7	148	68.5	123	82	263	96.3	608	84.7
p < 0.0001	Total	79	100	216	100	150	100	273	100	718	100
Local Boost	No	5	6.3	66	30.6	26	17.3	9	3.3	106	14.8
	Yes	74	93.7	150	69.4	124	82.7	264	96.7	612	85.2
p < 0.0001	Total	79	100	216	100	150	100	273	100	718	100
Local Boost Only	No	72	96	197	94.7	138	95.8	258	97	665	96
	Yes	3	4	11	5.3	6	4.2	8	3	28	4
p = 0.66	Total	75	100	208	100	144	100	266	100	693	100
CSI Dose	None	7	9.5	75	36.2	31	21.7	16	6	129	18.7
	< 30Gy	38	51.4	69	33.3	43	30.1	146	54.9	296	42.9
	> 30Gy	29	39.2	63	30.4	69	48.2	104	39.1	265	38.4
p < 0.0001	Total	74	100	207	100	143	100	266	100	690	100
Chemotherapy	No	11	13.4	16	7.1	9	5.9	14	5	50	6.8
	Yes	71	86.6	210	92.9	143	94.1	264	95	688	93.2
p = 0.09	Total	82	100	226	100	152	100	278	100	738	100
M status	M0	62	83.8	176	76.2	76	49.4	188	68.1	502	68.3
	M+	12	16.2	55	23.8	78	50.6	88	31.9	233	31.7
p < 0.0001	Total	74	100	231	100	154	100	276	100	735	100

Variable		WNT	%	SHH	%	Group 3	%	Group 4	%	Total	%
North America/Australia	Yes	43	50	124	51.2	91	55.8	146	49.3	404	51.3
	No	43	50	118	48.8	72	44.2	150	50.7	383	48.7
p = 0.6	Total	86	100	242	100	163	100	296	100	787	100

CSI = craniospinal irradiation

Table 2

PFS Multivariable Cox Model, All Patients

	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	p
Extent of Resection	Reference: GTR			
NTR	1.05	0.71	1.53	0.81581
STR	1.45	1.07	1.96	0.01567
Subgroup	Reference: Group 3			
WNT	0.27	0.14	0.54	0.00017
SHH	0.59	0.41	0.84	0.00322
Group 4	0.72	0.52	0.99	0.04114
M+ vs. M0	1.67	1.25	2.22	0.00048
Age	1	0.98	1.02	0.74057
Chemotherapy vs. No Chemotherapy	0.76	0.43	1.35	0.35286
Craniospinal Irradiation	Reference: None			
< 30Gy	0.42	0.29	0.61	< 0.0001
> 30Gy	0.45	0.31	0.65	< 0.0001
North America/Australia, No vs. Yes	1.47	1.14	1.9	0.00281

n = 738

Table 3

OS Multivariable Cox Model, All Patients

	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	p
Extent of Resection	Reference: GTR			
NTR	1.14	0.75	1.72	0.54837
STR	1.23	0.87	1.72	0.23879
Subgroup	Reference: Group 3			
WNT	0.25	0.12	0.53	0.00032
SHH	0.58	0.40	0.84	0.00377
Group 4	0.54	0.38	0.77	0.00062
M+ vs. M0	2.02	1.46	2.79	< 0.0001
Age	0.99	0.97	1.02	0.58044
Chemotherapy vs. No Chemotherapy	0.60	0.33	1.10	0.10005
Craniospinal Irradiation	Reference: None			
< 30Gy	0.48	0.32	0.73	0.00055
> 30Gy	0.53	0.36	0.79	0.00171
North America/Australia, No vs. Yes	1.72	1.29	2.29	0.00020

n = 778