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Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis

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Summary

Background Patients with incomplete surgical resection of medulloblastoma are controversially regarded as having a marker of high-risk disease, which leads to patients undergoing aggressive surgical resections, so-called second-look surgeries, and intensified chemoradiotherapy. All previous studies assessing the clinical importance of extent of resection have not accounted for molecular subgroup. We analysed the prognostic value of extent of resection in a subgroup-specific manner.

Methods We retrospectively identified patients who had a histological diagnosis of medulloblastoma and complete data about extent of resection and survival from centres participating in the Medulloblastoma Advanced Genomics International Consortium. We collected from resections done between April, 1997, and February, 2013, at 35 international institutions. We established medulloblastoma subgroup affiliation by gene expression profiling on frozen or formalin-fixed paraffin-embedded tissues. We classified extent of resection on the basis of postoperative imaging as gross total resection (no residual tumour), near-total resection (<1.5 cm² tumour remaining), or sub-total resection (≥1.5 cm² tumour remaining). We did multivariable analyses of overall survival and progression-free survival using the variables molecular subgroup (WNT, SHH, group 4, and group 3), age (<3 vs ≥3 years old), metastatic status (metastases vs no metastases), geographical location of therapy (North America/Australia vs rest of the world), receipt of chemotherapy (yes vs no) and receipt of craniospinal irradiation (<30 Gy or >30 Gy vs no craniospinal irradiation). The primary analysis outcome was the effect of extent of resection by molecular subgroup and the effects of other clinical variables on overall and progression-free survival.

Findings We included 787 patients with medulloblastoma (86 with WNT tumours, 242 with SHH tumours, 163 with group 3 tumours, and 296 with group 4 tumours) in our multivariable Cox models of progression-free and overall survival. We found that the prognostic benefit of increased extent of resection for patients with medulloblastoma is attenuated after molecular subgroup affiliation is taken into account. We identified a progression-free survival benefit for gross total resection over sub-total resection (hazard ratio [HR] 1.45, 95% CI 1.07–1.96, p=0.16) but no overall survival benefit (HR 1.23, 0.87–1.72, p=0.24). We saw no progression-free survival or overall survival benefit for gross total resection compared with near-total resection (HR 1.05, 0.71–1.53, p=0.8158 for progression-free survival and HR 1.14, 0.75–1.72, p=0.55 for overall survival). No significant survival benefit existed for greater extent of resection for patients with WNT, SHH, or group 3 tumours (HR 1.03, 0.67–1.58, p=0.89 for sub-total resection vs gross total resection). For patients with group 4 tumours, gross total resection conferred a benefit to progression-free survival compared with sub-total resection (HR 1.97, 1.22–3.17, p=0.0056), especially for those with metastatic disease (HR 2.22, 1.00–4.93, p=0.050). However, gross total resection had no effect on overall survival compared with sub-total resection in patients with group 4 tumours (HR 1.67, 0.93–2.99, p=0.084).

Interpretation The prognostic benefit of increased extent of resection for patients with medulloblastoma is attenuated after molecular subgroup affiliation is taken into account. Although maximum 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 because there is no definitive benefit to gross total resection compared with near-total resection.

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Introduction

Current clinical risk stratification for patients with medulloblastoma separates children into average-risk and high-risk strata. High-risk disease is defined by the presence of metastases at diagnosis, age less than 3 years, and residual disease of at least 1.5 cm².¹⁻⁵ In the scientific literature, the prognostic benefit of gross total resection versus sub-total resection or biopsy (appendix pp 44-46) is controversial.^{1,2,6-14} Many patients with 1.5 cm² or more of residual disease either have to undergo so-called second-look surgery to achieve a gross total resection or are treated with high-risk protocols including higher doses of craniospinal irradiation and more intensive chemotherapy.^{2,15}

Aggressive resection of medulloblastoma might be associated with increased surgical complications. Post-surgical neurological morbidity for children with medulloblastoma, irrespective of the extent of residual tumour, is 24% and can increase to as high as 44% after gross total resection.^{16,17} The incidence of posterior fossa syndrome (cerebellar mutism) might be increased after gross total resection compared with less complete resections.¹⁸ Most 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 (ie, the brainstem) can greatly increase morbidity.^{21,22} Establishing the appropriate balance between extent of resection and respect for critical structures while achieving the best prognosis is an ongoing challenge in neurosurgery and neuro-oncology.

Medulloblastoma is no longer considered a single entity, but rather consists of four distinct molecular subgroups (WNT, SHH, group 3, and group 4) with distinct demographics, clinical features including prognosis, transcriptomes, and genetics.^{4,23-31} Crucially, all previous studies of the prognostic importance of extent of resection for medulloblastoma have been done without knowledge of subgroup affiliation (see appendix pp 44-46). We retrospectively analysed the prognostic value of extent of resection in a subgroup-specific manner in patients treated at centres participating in the Medulloblastoma Advanced Genomics International Consortium.

Methods

Specimen processing and subgroup identification

Surgical resections took place from April, 1997, to February, 2013, at the Hospital for Sick Children and our 34 collaborating institutions (35 centres in total). Patients were deemed ineligible for study inclusion if they had incomplete data about molecular subgroup, extent of

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Research in context

Evidence before this study

On Jan 30, 2014, we searched PubMed with the search terms "resection" and "medulloblastoma". This search resulted in 285 articles. Only studies in humans written in English were included. We reviewed article titles and abstracts for relevancy. We included review articles, case reports, articles including patients older than 18 years, articles including tumours other than medulloblastoma, and articles including patients with supratentorial tumour locations. We also excluded articles in which no statistical comparison of extent of resection was made or articles from the same institution with duplicated patient data. This resulted in 36 articles, which were a combination of reports either reporting clinical trials, or a post-hoc analysis evaluating incomplete resection as a prognostic marker. We found 12 articles supporting increased extent of resection associated with an improved prognosis, 12 articles showing no survival benefit with increased extent of resection, and 12 articles showing an indeterminate effect of increased extent of resection.

Added value of this study

To our knowledge, our international study of 787 patients with medulloblastoma is the largest and most comprehensive so far to analyse the importance of extent of resection on survival in a

subgroup-specific manner. This compares with a median patient number of 80 in other studies that address the clinical importance of extent of resection in children with medulloblastoma. Our results do not show a definitive association between extent of resection and survival in patients with WNT, SHH, and group 3 medulloblastomas. There was a survival benefit for gross total resection compared with sub-total resection with group 4 medulloblastomas, especially for patients with metastatic disease.

Implications of all the available evidence

The current goal of surgical resection in paediatric patients with medulloblastoma who are older than 3 years and have no metastases is a postoperative residual area of less than 1.5 cm². When we accounted for subgroup, there was a progression-free survival benefit for gross total resection compared with a sub-total (≥ 1.5 cm²) resection, but we found no definitive prognostic benefit for a gross total resection instead of a near-total resection (< 1.5 cm²). Our findings will substantially affect surgical practice because overly aggressive surgical resection with resultant neurological morbidity can potentially be avoided. Additionally, the value of increased craniospinal radiation for patients with more than 1.5 cm² residual tumour should be questioned and explored in future prospective trials.

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resection, or survival. Medulloblastoma specimens were sterilely stored (frozen or formalin-fixed paraffin-embedded tissues) at each institution in accordance with the Ethics Review Board of the Hospital for Sick Children and the individual institutions. Each centre provided information and specimens for one to 139 patients (appendix p 47). The largest ten centres provided 505 (64%) of 787 specimens. Between one and six different surgeons from each institution performed tumour resections. By extrapolating from the experience at the Hospital for Sick Children, which has one of the highest surgical volumes in North America, we estimated that each surgeon would have operated on less than 20 patients. Therefore, adjusting for surgeon in the multivariable analysis was not feasible, especially for institutions that contributed small numbers of patients. Although a small overlap exists with a previously published report from our group with respect to overall survival and cytogenetics,³² we know of no 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. The molecular subgroup of tumours was established by use of NanoString limited gene expression profiling (NanoString Technologies, Seattle, WA, USA) on specimens weeks to years after surgical resection.^{33,34}

Extent of resection

At each contributing institution, extent of resection was established based on surgeons' reports and confirmed on postoperative gadolinium-enhanced T1-weighted MRI, or less commonly contrast-enhanced CT. The non-centralised radiographic review was masked to molecular subgroup. Based on postoperative imaging, we defined gross total resection as no residual tumour, near-total resection as less than 1.5 cm² residual tumour, and sub-total resection as 1.5 cm² or more of residual tumour.^{1,2}

Statistical analysis

The primary analysis outcome was the effect of extent of resection by molecular subgroup and the effects of other clinical variables on overall and progression-free survival. We tested for association between extent of resection and clinicopathological variables with Fisher's exact test. We used log-rank tests to compare groups in terms of survival. We used univariate and multivariable Cox proportional hazard regression to estimate hazard ratios (HR) for progression-free survival and overall survival, including 95% CIs. The variables we included were molecular subgroup (WNT, SHH, group 3, and group 4), age (<3 vs ≥3 years old), metastatic status (yes vs no), geographical location of therapy (North America/Australia vs rest of the world), receipt of chemotherapy (yes vs no), and receipt of craniospinal irradiation (<30 Gy or >30 Gy vs no craniospinal irradiation). For all multivariable Cox regression models, we accounted for missing data for covariables by use of multiple imputations. To do imputations, we used predictive mean matching based on

50 bootstrap samples with five burn-in iterations. This approach works for continuous, binary, and categorical predictors. Briefly, in each bootstrap sample, missing data for each variable was predicted conditional on all other variables. For each imputed dataset, a multivariable Cox regression model is fitted. Estimates from all imputed datasets are then combined in a weighted approach to get final Cox regression model estimates. Imputations were done with R package Hmisc function aregImpute version 3.17-2.³⁵

We generated nomograms of multivariable models with R package rms version 4-4-2. We used forest plots to show the HRs of different extents of resection in various subgroups. To account for adjuvant chemotherapy and radiation differences, we stratified or adjusted tests on difference in survival for location with respect to North America and Australia (Children's Oncology Group [COG] members) versus the rest of the world, mainly because of the uniformity of risk-adapted therapy from COG-affiliated centres compared with more heterogeneous treatment across the remaining worldwide centres. We analysed chemotherapy and radiation at diagnosis, but we did not analyse treatment regimen at recurrence because of the small proportion of patients whose disease progressed and the heterogeneity of salvage therapy between the 35 collaborating institutions. We analysed metastatic status as the presence or absence of metastases at diagnosis to simplify the multivariable analysis, especially in view of the fact that patients were divided into four molecular subgroups. This is consistent with another recent study that accounted for medulloblastoma subgroup.³⁶ We used interaction tests in Cox regression to formally assess the heterogeneity of the effect of extent of resection between molecular subgroups. We assessed the quantitative covariate age for non-linear functional association using Martingale residuals without indication of a violation. We then confirmed that multivariable fractional polynomials or restricted cubic splines would not improve the fit of age in the model. All tests were two-sided. We judged p values less than 0.05 to be significant. We did survival analysis by use of the R package survival (version 2.37) and ggplot2 (version 0.9.3.1). We did all analyses in the R statistical environment (version 3.1.3).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, we analysed a cohort of 787 patients (table 1, appendix pp 21–42). Complete data were available and analysed for 628 patients for all covariables used in multivariable Cox regression (table 1). 86 patients had

WNT tumours, 242 had SHH tumours, 163 had group 3 tumours, and 296 had group 4 tumours. 159 sub-total resections, 109 near-total resections, and 519 gross total resections were included. We detected no significant difference in distribution of gross total resection, near-total resection, and sub-total resection operations between the four molecular subgroups ($p=0.076$). For progression-free survival analysis, 287 events were recorded in 738 patients (12 in patients with WNT tumours, 92 with SHH, 76 with group 3, and 107 with group 4). For overall survival analysis, 253 of 778 patients died (11 with WNT tumours, 82 with SHH, 73 with group 3, and 87 with group 4). Patients with incomplete survival data originated from 14 different centres and no pattern of missing data existed. In the overall survival analysis, 201 (54%) of 778 patients died during the first 5 years of follow-up (median follow-up 1.83 years, IQR 1.83–7.5) and 413 (72%) patients had 3-year follow-up. In the progression-free survival analysis, 263 (54%) of 487 patients without an event (progression) were alive at 5 years of follow-up and 347 (71%) patients had 3-year follow-up (median time to progression 3.08 years, IQR 1.49–7.00). To compare our cohort with previously published studies, we calculated the prognostic value of extent of resection without accounting for subgroup, and we were able to replicate previous results that showed a benefit for increased extent of resection (sub-total resection *vs* gross total resection) in terms of both progression-free survival (65.4%, 95% CI 60.9–70.2 for gross total resection *vs* 47.2%, 39.1–57.1 for sub-total resection, HR 1.8, 1.3–2.4, $p<0.0001$) and overall survival (72.6%, 95% CI 68.4–77.1 for gross total resection *vs* 60.6%, 95% CI 52.8–69.6, sub-total resection, HR 1.6, 1.2–2.2, $p=0.010$; figure 1) across the whole population not stratified by molecular subgroup.^{1,2,8} We conclude that our cohort is similar to previously published cohorts. Similar to previous studies that have included molecular subgroups of medulloblastoma, patients with WNT tumours had the best progression-free survival and overall survival (figure 1), followed by group 4 and SHH, then group 3. Median survival could not be calculated for progression-free survival or overall survival because survival did not reach 50%. 5-year progression-free survival was 87.6% (95% CI 80.3–95.6) for patients with WNT tumours, 63.1% (56.5–70.4) for SHH tumours, 54.6% (46.6–63.9) for group 3 tumours, and 59.4% (53.3–66.2) for group 4 tumours. 5-year overall survival was 89.9% (95% CI 83.5–96.8) for patients with WNT tumours, 71.1% (65.2–77.6) for SHH tumours, 55.3% (47.7–64.2) for group 3 tumours, and 71.3% (65.6–77.5) for group 4 tumours. We did no post-hoc comparisons on this univariate analysis of molecular subgroup and p values were calculated across all four subgroups.^{23,30,37}

We did a test on heterogeneity of the prognostic effect of extent of regression (appendix p 1). Notably, we detected

	WNT	SHH	Group 3	Group 4	p value
Extent of resection					
GTR	51 (59%)	162 (67%)	110 (67%)	196 (66%)	..
NTR	21 (24%)	24 (10%)	23 (14%)	41 (14%)	..
STR	14 (16%)	56 (23%)	30 (18%)	59 (20%)	..
Total	86 (100%)	242 (100%)	163 (100%)	296 (100%)	0.076
Sex					
Female	49 (60%)	90 (38%)	41 (26%)	81 (28%)	..
Male	33 (40%)	142 (61%)	118 (74%)	211 (72%)	..
Total	82 (100%)	232 (100%)	159 (100%)	292 (100%)	<0.0001
Age (years)					
<3	3 (4%)	79 (33%)	30 (19%)	9 (3%)	..
≥3	79 (96%)	158 (67%)	130 (81%)	283 (97%)	..
Total	82 (100%)	237 (100%)	160 (100%)	292 (100%)	<0.0001
Radiation					
No	5 (6%)	68 (31%)	27 (18%)	10 (4%)	..
Yes	74 (94%)	148 (69%)	123 (82%)	263 (96%)	..
Total	79 (100%)	216 (100%)	150 (100%)	273 (100%)	<0.0001
Local boost					
No	5 (6%)	66 (31%)	26 (17%)	9 (3%)	..
Yes	74 (94%)	150 (69%)	124 (83%)	264 (97%)	..
Total	79 (100%)	216 (100%)	150 (100%)	273 (100%)	<0.0001
Local boost only					
No	72 (96%)	197 (95%)	138 (96%)	258 (97%)	..
Yes	3 (4%)	11 (5%)	6 (4%)	8 (3%)	..
Total	75 (100%)	208 (100%)	144 (100%)	266 (100%)	0.66
CSI dose					
None	7 (9%)	75 (36%)	31 (22%)	16 (6%)	..
<30 Gy	38 (51%)	69 (33%)	43 (30%)	146 (55%)	..
>30 Gy	29 (39%)	63 (30%)	69 (48%)	104 (39%)	..
Total	74 (100%)	207 (100%)	143 (100%)	266 (100%)	<0.0001
Chemotherapy					
No	11 (13%)	16 (7%)	9 (6%)	14 (5%)	..
Yes	71 (87%)	210 (93%)	143 (94%)	264 (95%)	..
Total	82 (100%)	226 (100%)	152 (100%)	278 (100%)	0.085
Metastatic status					
Metastases absent	62 (84%)	176 (76%)	76 (49%)	188 (68%)	..
Metastases present	12 (16%)	55 (24%)	78 (51%)	88 (32%)	..
Total	74 (100%)	231 (100%)	154 (100%)	276 (100%)	<0.0001
North America or Australia					
Yes	43 (50%)	124 (51%)	91 (56%)	146 (49%)	..
No	43 (50%)	118 (49%)	72 (44%)	150 (51%)	..
Total	86 (100%)	242 (100%)	163 (100%)	296 (100%)	0.60

GTR=gross total resection. NTR=near-total resection. STR=sub-total resection. CSI=craniospinal irradiation.

Table 1: Patient characteristics by medulloblastoma molecular subgroup

no significant interaction between subgroup and extent of resection, suggesting that the effect of extent of resection is not significantly different between the subgroups (appendix p 1).

We subsequently did a multivariable analysis of progression-free survival and overall survival in a subgroup-specific manner. In patients with WNT tumours, the increase in risk of progression associated with sub-total

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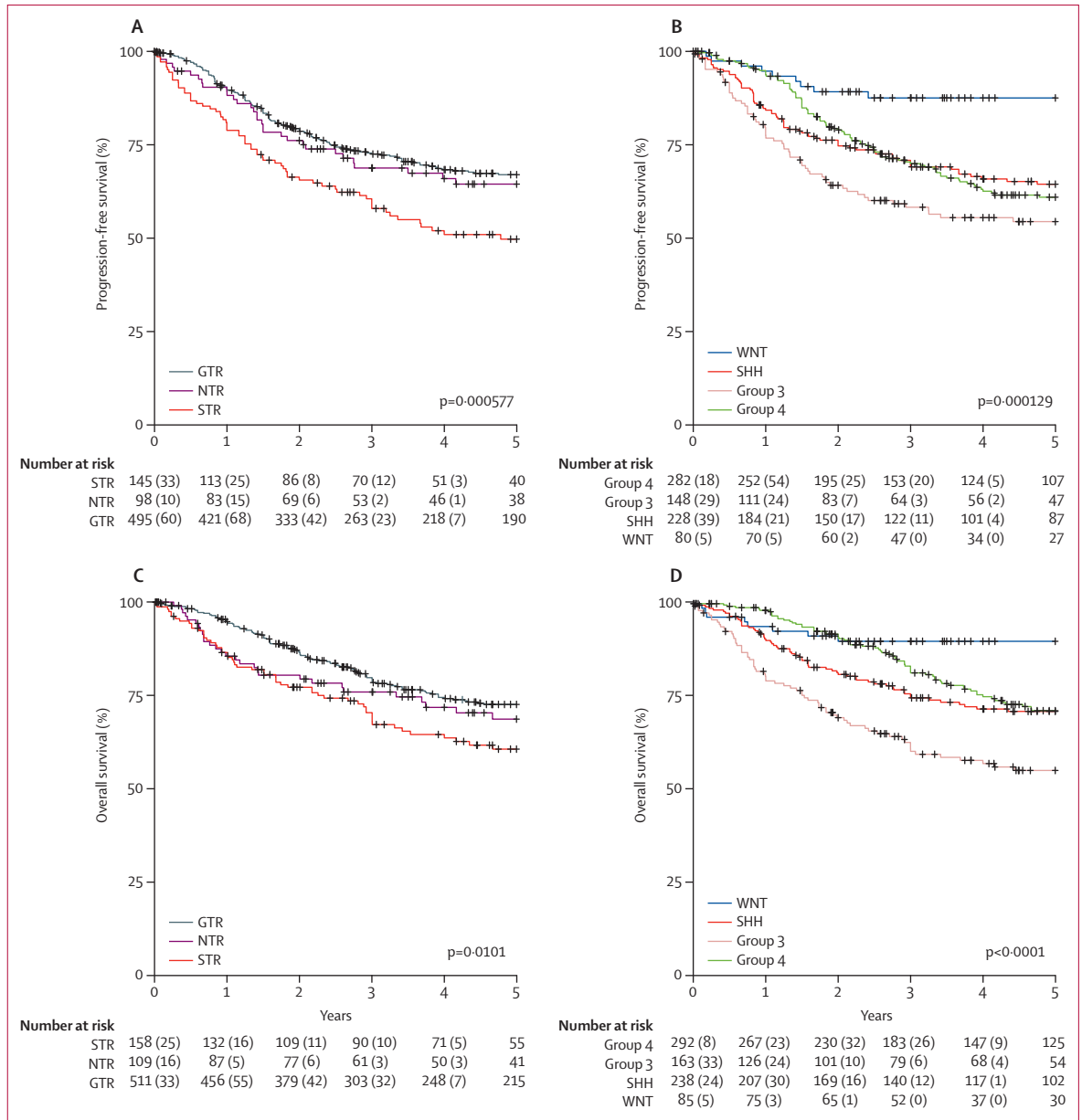
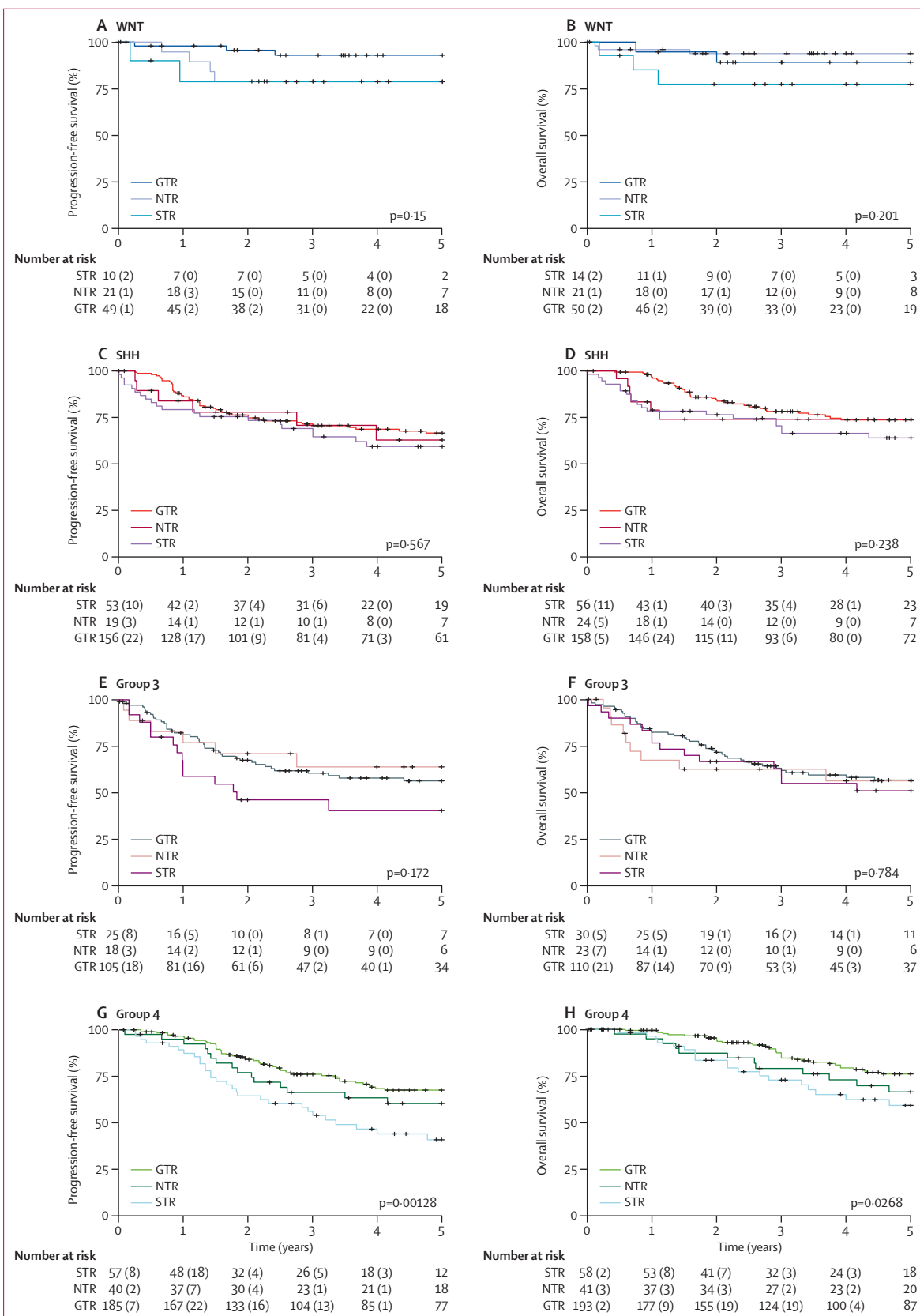


Figure 1: 5-year overall and progression-free survival for all patients Curves show progression-free survival (A, B) and overall survival (C, D) by extent of resection (A, C) and molecular subgroup (B, D). Values in parentheses show failure events during that time period. p values are log-rank across the four subgroups. GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.

resection (HR 3.04, 95% CI 0.40–23.30, $p=0.28$) and near-total resection (HR 1.91, 0.39–9.35, $p=0.43$) compared with gross total resection was not significant (appendix p 1). For overall survival, risk with sub-total resection (HR 2.40, 95% CI 0.26–22.09, $p=0.44$) and near-total resection (HR 0.90, 0.12–6.88, $p=0.92$) was not significantly different compared with gross total resection (appendix p 2). The implications of extent of resection for WNT patients are somewhat limited by the small cohort, which included only 14 sub-total resections and 21 near-total resection operations (figure 2; appendix p 43).

In a multivariable analysis of patients with SHH tumours, only metastatic status (HR 2.52, 95% CI 1.41–4.50, $p=0.0018$) and >30 Gy craniospinal radiation (HR 0.50, 0.25–0.99, $p=0.046$) were significantly associated with progression. Neither sub-total resection (HR 1.04, 0.6–1.81, $p=0.88$) nor near-total resection

Figure 2: 5-year survival for extent of resection by subgroup Molecular subgroups are WNT (A, B), SHH (C, D), group 3 (E, F), and group 4 (G, H). Numbers in parentheses are failure events during that time period. p values are log-rank test across the three strata (GTR vs NTR vs STR). GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.



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See Online for appendix

	Hazard ratio (95% CI)	p value
Extent of resection vs GTR		
NTR	1.05 (0.71–1.53)	0.81581
STR	1.45 (1.07–1.96)	0.01567
Molecular subgroup vs 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
Metastases present vs metastases absent		
Age (≥3 vs <3 years)	1.00 (0.98–1.02)	0.74057
Chemotherapy vs no chemotherapy	0.76 (0.43–1.35)	0.35286
Craniospinal irradiation vs no irradiation		
<30 Gy	0.42 (0.29–0.61)	<0.0001
>30 Gy	0.45 (0.31–0.65)	<0.0001
North America/Australia (no vs yes)	1.47 (1.14–1.9)	0.00281

GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.

Table 2: Progression-free survival by multivariable Cox model for all patients (n=738)

	Hazard ratio (95% CI)	p value
Extent of resection vs GTR		
NTR	1.14 (0.75–1.72)	0.54837
STR	1.23 (0.87–1.72)	0.23879
Molecular subgroup vs 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
Metastases present vs metastases absent		
Age (≥3 vs <3 years)	0.99 (0.97–1.02)	0.58044
Chemotherapy vs no chemotherapy	0.60 (0.33–1.10)	0.10005
Craniospinal irradiation vs no irradiation		
<30 Gy	0.48 (0.32–0.73)	0.00055
>30 Gy	0.53 (0.36–0.79)	0.00171
North America/Australia, (no vs yes)	1.72 (1.29–2.29)	0.00020

GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.

Table 3: Overall survival by multivariable Cox model for all patients (n=778)

(HR 0.82, 0.35–1.92, p=0.65) were associated with an increased risk of progression in patients with SHH tumours compared with gross total resection (appendix p 3). Similarly, for overall survival, only metastatic status was significant (HR 2.52, 95% CI 1.72–6.04, p=0.00026), and neither sub-total resection (HR 1.06, 95% CI 0.57–1.96, p=0.85) nor near-total resection (HR 0.78, 0.31–1.95, p=0.59) were associated with reduced overall survival compared with gross total resection (appendix p 4). In both a univariable and multivariable model, in which we stratified patients with SHH tumours by metastatic status, we detected no significant difference in survival with sub-total resection (appendix pp 48–49).

For patients with group 3 tumours, metastatic status (HR 2.27, 95% CI 1.27–4.05, p=0.0055) and craniospinal radiation more than 30 Gy (HR 0.37, 95% CI 0.19–0.71, p=0.0030) were significantly associated with progression risk. Neither sub-total resection (HR 1.20, 95% CI 0.64–2.27, p=0.57) nor near-total resection (HR 0.61, 0.27–1.40, p=0.25) were significantly associated with progression for patients with group 3 tumours compared with gross total resection (appendix p 5). Variables associated with reduced overall survival were metastatic status (HR 2.19, 95% CI 1.22–3.90, p=0.0082), age (HR 0.90, 95% CI 0.82–0.98, p=0.020), and chemotherapy (HR 0.29, 95% CI 0.11–0.77, p=0.013). We identified no increased risk of death due to sub-total resection (HR 0.84, 95% CI 0.44–1.61, p=0.60) or near-total resection compared to gross total resection (HR 0.81, 0.38–1.73, p=0.59; appendix p 6). In both a multivariable and univariable model, in which we stratified patients with group 3 tumours by metastatic status, we detected no significant difference in survival with subtotal resection (appendix pp 48–49).

For patients with group 4 tumours, variables associated with progression risk were sub-total resection (HR 1.97, 95% CI 1.22–3.17, p=0.0056), less than 30 Gy of craniospinal radiation (HR 0.44, 95% CI 0.21–0.91, p=0.028), and geographical treatment location (HR 1.99, 1.29–3.08, 0.0019), whereas near-total resection was not significant (HR 1.24, 0.70–2.20, p=0.45; appendix p 7) compared with gross total resection. We identified no increased risk for death with sub-total resection (HR 1.67, 0.93–2.99, p=0.084) and near-total resection compared to gross total resection (HR 1.38, 0.71–2.71, p=0.34; appendix p 8). Subgroup analyses for patients with or without metastatic disease showed that the significantly increased risk of progression following a sub-total resection in group 4 was restricted to patients with metastatic disease (appendix pp 8–10, 49). Specifically, in a multivariable model using age, craniospinal radiation and site of treatment, the non-significant benefits of increased extent of resection for progression-free survival and overall survival were largely restricted to patients with metastases at baseline (for progression-free survival, HR 1.36, 0.67–2.75, p=0.39 for patients without metastases vs HR 2.22, 1.00–4.93, p=0.050 patients with metastases; for overall survival, HR 1.29, 0.52–3.17, p=0.59 for patients without metastases vs HR 2.09, 0.79–5.59, p=0.14 for patients with metastases; appendix pp 48–49). When the multivariable analysis was restricted only to non-group 4 tumours, we found no difference between gross total resection and sub-total resection for either progression-free survival (HR 1.15, 95% CI 0.77–1.71, p=0.49) or overall survival (HR 1.03, 95% CI 0.67–1.58, p=0.89; appendix pp 11–12).

We then did multivariable analyses with respect to metastatic status and age. In patients without metastases, variables associated with progression risk were geographical location of treatment, molecular subgroup, and craniospinal radiation. Neither near-total resection nor sub-total resection (appendix p 13) were associated with an increased progression risk. Variables associated with risk of death were geographical treatment location, subgroup, and craniospinal radiation. For overall survival, neither near-total nor sub-total resection (were associated with increased risk (appendix p 14). In patients with metastases, variables associated with progression risk were molecular subgroup, craniospinal radiation, and geographical treatment location. Neither near-total resection nor sub-total resection were associated with increased progression-free survival (appendix p 15). Variables associated with risk of death were molecular subgroup and chemotherapy. Neither near-total resection nor sub-total resection were associated with an increased risk of death (appendix p 16).

A significant interaction existed between age and extent of resection ($p=0.03$ for progression-free survival, $p=0.01$ for overall survival; appendix p 1), suggesting that the prognostic effect of sub-total resection might differ in patients aged less than 3 years and 3 years and older. In the 121 patients younger than 3 years (who almost exclusively had SHH [$n=79$] and group 3 tumours [$n=30$]), molecular subgroup was associated with risk of progression, whereas neither near-total gross resection nor sub-total resection were associated with increased risk of progression (appendix p 17). Similarly, neither near-total gross resection nor sub-total resection were associated with increased risk of death (appendix p 18). In a multivariate analysis of patients aged 3 years or older, for both progression-free survival and overall survival, near-total resection was not prognostic however, sub-total resection was prognostic. Molecular subgroup conferred a significant risk of both progression and death (appendix pp 19–20).

Multivariable analysis across all patients showed sub-total resection, molecular subgroup, metastatic status, receiving craniospinal radiation, and geographical location to be significant predictors of progression-free survival; near-total resection had no increased risk of progression (table 2). Multivariable analysis of overall survival identified significant associations with molecular subgroup, metastatic status, craniospinal radiation, and geographic location (table 3). Nomograms of the multivariable model to show the relative clinical effect of each variable to predict progression-free survival and overall survival at 3 and 5 years are shown in figure 3. An example of nomogram use is shown in the appendix (p 53).

We did multivariable direct comparisons of gross total resection, near-total resection, and sub-total resection for both progression-free survival and overall survival both for the entire population, and within each molecular

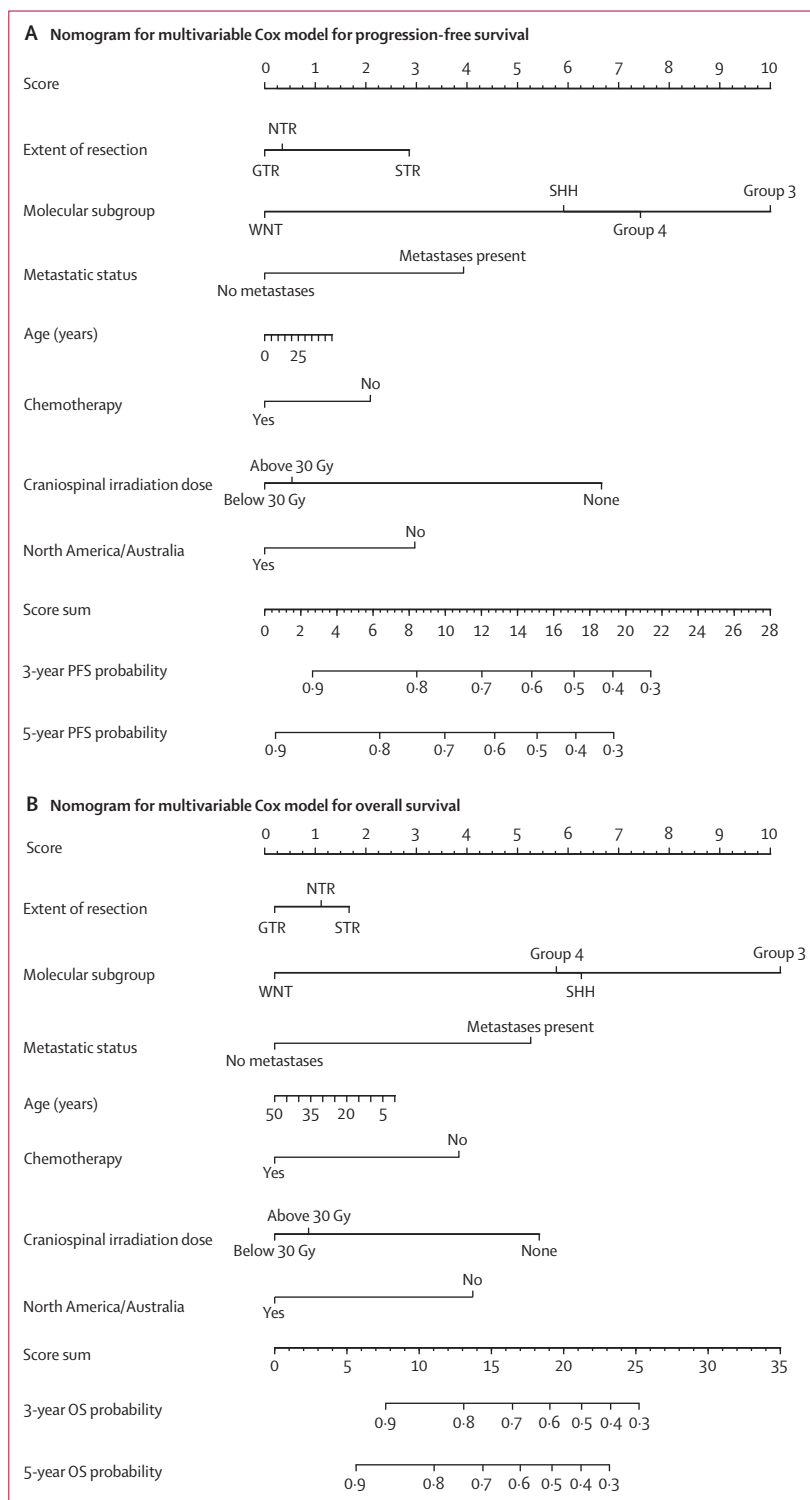


Figure 3: Survival nomograms

Nomograms were created from the multivariable Cox model. The presence or absence of each variable is scored (top row). The cumulative score from each variable is used to calculate 3-year and 5-year PFS (A) and OS (B) probabilities. PFS=progression-free survival. OS=overall survival. GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.

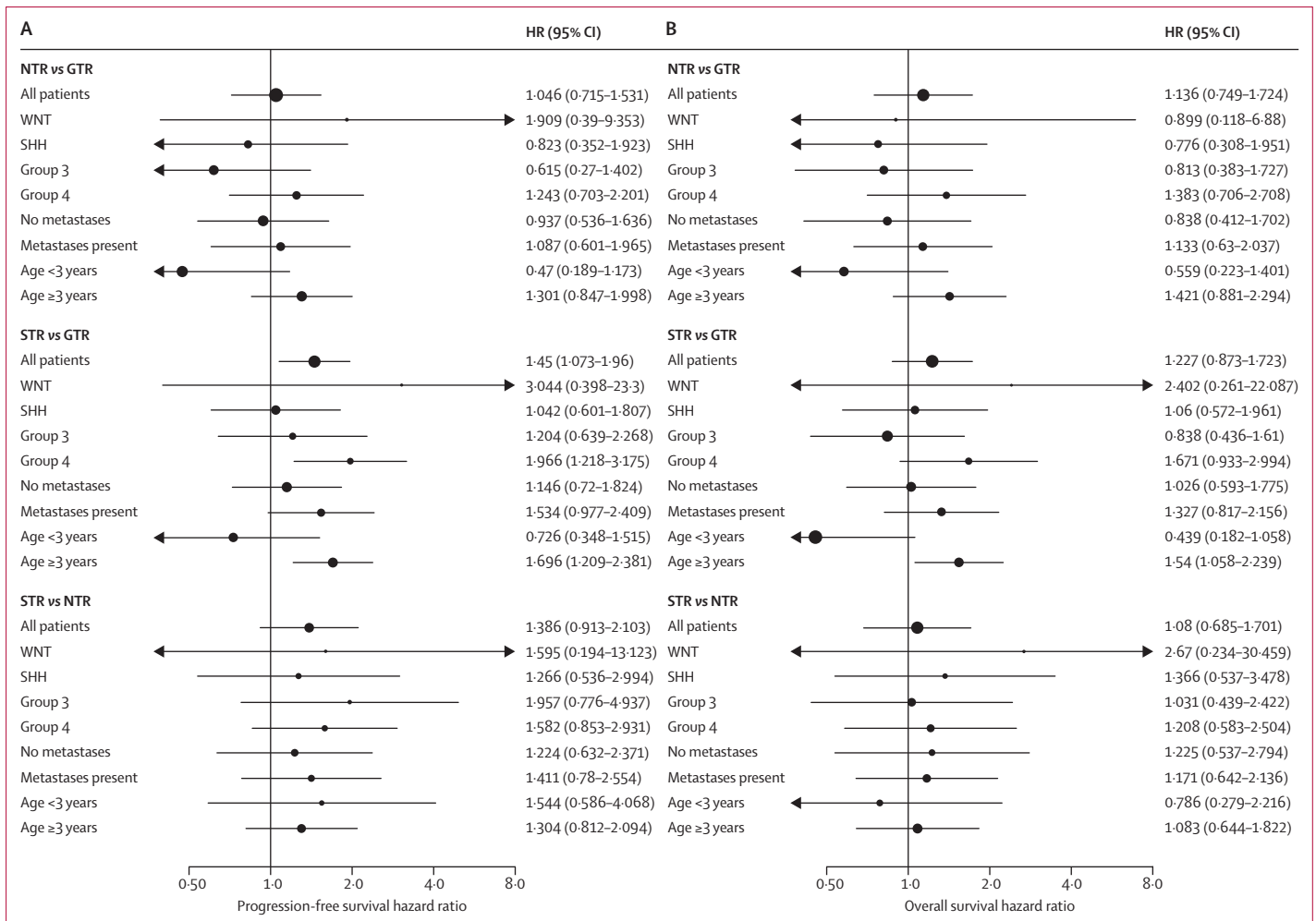


Figure 4: Effect of extent of resection in patient subgroups

Multivariable forest plots directly compare extent of resection for PFS (A) and OS (B). Circles to the right of the vertical line show increased risk while those to the left of the vertical line show decreased risk. HR=hazard ratio. GTR=gross total resection. NTR=near-total resection. STR=sub-total resection.

subgroup (figure 4). No subgroups were identified as having a significantly increased risk of progression in comparisons of near-total resection versus gross total resection. For sub-total resection versus gross total resection, we saw that sub-total resection confers a progression risk for the entire cohort, patients with group 4 tumours, and patients aged 3 years or older (figure 4). The patients with metastases and group 4 tumours are possibly driving these age-related effects, because there were no observable effects for patients with WNT, SHH, or group 3 tumours. The same analysis for overall survival did not show a difference between sub-total resection and gross total resection for patients with group 4 tumours (figure 4). Unexpectedly, for patients younger than 3 years, gross total resection and near-total resection do not improve survival compared with sub-total resection (figure 4). Univariate analysis and multivariable analysis adjusted only for chemotherapy and radiotherapy regimens showed similar results

(appendix p 51). A sensitivity analysis of random effects and institution showed similar results with and without accounting for institution (appendix p 43).

Discussion

Our main findings are that the benefit of increased extent of resection is largely attenuated after molecular subgroup is taken into account; that near-total resection seems to be prognostically equivalent to gross total resection, and that the magnitude of the beneficial clinical effect of gross total resection on prognosis is smaller than those of other known risk factors for medulloblastoma. To our knowledge, this study assesses the largest cohort of patients so far with respect to role of extent of resection in the treatment of medulloblastoma.

The current goal of surgical resection for patients with medulloblastoma is to achieve a safe gross total resection without significant neurological sequelae. If the tumour is adherent to critical structures, the goal is to leave a

residual of less than 1.5 cm², a near-total resection.²¹ There is a controversial general perception in the neurosurgical community that a gross total resection is prognostically superior to a near-total resection. Our findings in this study show that there is no prognostic difference between gross total resection and near-total resection and should help to convince surgeons to minimise morbidity when removing small residual portions of tumours adherent to critical structures. Sub-total resection can range from slightly larger than 1.5 cm² up to small limited needle biopsies. This value of less than 1.5 cm² was based mainly on postoperative CT scans,¹² which had relatively low resolution compared with modern MRI. The value was established as part of CCG921,² which ran in the late 1980s when treatment and outcomes were substantially different compared with modern cisplatin-based therapy, and during which the histological classification probably included other entities such as atypical teratoid rhabdoid tumours. Furthermore, about half of medulloblastomas (mostly group 4) do not enhance on MRI or have heterogeneous enhancement.³⁸ Non-enhancing residual tumour can easily be missed even on modern postoperative MRI, especially 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 establish exactly how much size of residual tumour is truly predictive of a poor prognosis.

There are several reasons why our data showing no definitive association between extent of resection and survival are not surprising. Review of the scientific literature revealed a roughly equal number of studies that did and did not identify an association between increased extent of resection and overall survival (appendix p 44–46). Despite clinical uncertainty that is arguably justified by the existing evidence, most neurosurgeons attempt a maximum safe gross total resection in an attempt to maximise progression-free survival and overall survival in the absence of more definitive data.

Previous prospective clinical trials have cast doubt on the role of extent of resection for children with medulloblastoma. Packer and colleagues⁵ reported a 5-year event-free survival of 83% (SE 2.2) in patients without metastases with less than 1.5 cm² residual tumour (n=313) compared with 75% (SE 13) in patients without metastases with 1.5 cm² or more (n=15), despite both groups having received only 23.4 Gy of craniospinal irradiation. Gajjar and colleagues reported that, at a median follow-up of more than 8 years, zero of six patients with residual tumour larger than 1.5 cm² treated as high risk in the St Jude Medulloblastoma-96 cohort³⁶ had evidence of disease.³ The HIT2000³⁶ multicentre clinical trial cohort did not show an association between residual tumour larger than 1.5 cm² and event-free survival. The SIOP PNET4 study,³⁹ which did not include molecular subgroup information, defined non-metastatic, sub-totally resected tumours as average-risk disease and reported that sub-total

resection was the strongest negative prognostic factor, although this finding was limited by the fact that only 31 (9%) of 340 patients had a residual of 1.5 cm² or larger. Finally, we previously reported³⁴ that in patients with group 3 and 4 medulloblastoma, the site of recurrence is almost always metastatic and not the local tumour bed. In patients with group 4 tumours, the benefit of gross total resection seemed to be mostly restricted to patients with metastases, rather than patients without metastases who receive intensified craniospinal irradiation when residual disease exceeds 1.5 cm². Why patients with metastatic group 4 tumours seem to have reduced survival with sub-total resection is unclear, but the simplest proximate explanation is that the degree of metastatic dissemination is higher in this group than in the others, hence surgeons have a reduced impetus to pursue an aggressive resection. Among patients who have undergone sub-total resection, the average residual tumour size might also be larger for patients with metastases than for patients without.

We would like to emphasise 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 whereby a small diagnostic biopsy is done followed by adjuvant therapy, because the type of disease for which this is appropriate is seldom seen and was not included in our dataset. The clinical application of our findings might be restricted at presentation because the subgroup of the patient's tumour is not usually known definitively at the time of surgery. However, our results could certainly inform the value of second-look surgery for small residual tumours.

At many institutions worldwide, patients are deemed to be at high risk if they have 1.5 cm² or more residual tumour on postoperative MRI. This classification has profound implications with respect to the amount of adjuvant craniospinal radiation these patients receive (36 Gy compared with the 23 Gy received by patients at average risk at most COG and International Society of Paediatric Oncology-associated centres). Notably, patients from COG centres in North America and Australia in this study had significantly better progression-free survival and overall survival than did those treated at non-COG centres, possibly because of the uniform adjuvant cerebrospinal irradiation protocols in the North American and Australian centres and heterogeneous treatment in the worldwide cohort. There is a well reported decrease in long-term IQ and quality of life in patients who receive high-dose craniospinal irradiation compared with low-dose treatment.⁴⁰ In the present study, we did not see a definitive association between increased extent of resection and progression-free survival or overall survival in patients with WNT, SHH, and group 3 medulloblastoma. A small subset of SHH group tumours show extensive nodular histology (MBEN),²⁴ which has been shown to have the most

favourable prognosis of all histological types⁷ and typically occurs in infants (aged <3 years).⁴¹ Garre and colleagues⁴¹ reported that residual tumour of 1·5 cm² or larger was not significantly associated with overall survival in patients with very large MBEN tumours caused by familial tumour predisposition syndromes. In patients with group 4 medulloblastoma, and patients aged 3 years or older, aggressive resections might have role in achieving residual disease smaller than 1·5 cm², although the relative benefit for overall survival is indeterminate and should be weighed against the risks associated with aggressive surgical resection. Clinicians might need to weigh the small overall survival risk of residual disease against the marked risk of poor long-term quality of life when deciding whether to initiate high-dose craniospinal radiotherapy for patients without metastases who have residual disease.

Limitations of our study include the absence of 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 that accounts for molecular subgroup and randomly assigns patients to less than 1·5 cm² residual or aggressive debulking while leaving at least 1·5 cm² residual would be the gold standard to clarify the role of sub-total resection. However, such a study would be both ethically and practically impossible to achieve. Assuming survival rates similar to those in our cohort and based on the HR from our multivariable analysis, in a trial with 3 years of recruitment and a minimum of 3 years follow-up, one-sided α 2·5, β 0·2, and clinical acceptable non-inferiority margin of 1·2 for the HR for the upper confidence limit, more than 6400 patients would be needed. Our present study contains 787 patients with medulloblastoma, which is, to our knowledge, the largest cohort so far in which the value of the extent of resection has been assessed and it contains the largest number of incompletely resected medulloblastomas yet analysed. Although we are unable to definitively exclude a small, significant benefit for gross total resection, we point out that the benefit of increased extent of resection has never been definitively shown in a proper randomised trial, and that if our data for extent of resection were instead for a novel drug or therapy, this novel therapy would be rejected out of hand even if it had minimal side-effects. Any potential age-related differences with respect to the clinical importance of extent of resection need further investigation in a prospective randomised trial.

We conclude that although the primary goal of surgery should be gross total resection, no prognostic difference exists between near-total resection and gross total resection, therefore, gross total resection should not be pursued instead of near-total resection if there is clinical risk of neurological sequelae. These data question the clinical benefit of second-look surgery for small residual WNT, SHH, or group 3 medulloblastomas because of the

possible morbidity of surgery and the delay in the commencement of radiation. Both previous studies and our results question the statistical significance and clinical magnitude of effect for the use of residual disease as a criterion to classify patients as high risk and precipitate high-dose craniospinal radiotherapy. Our data suggest an urgent need to revisit residual disease as a risk stratification criterion, especially since more informative and robust molecular markers have been described and validated.

Contributors

EMT, THi, VR, EB, and MDT designed the study. MDT procured financial support. EMT, VR, MR, BLu, S-KK, JYL, AANR, CG, KKWL, H-KN, TK, WAG, MP-P, SP, Y-JC, JM, IFP, RLH, SL, WJI, ARH, AJo, MF-M, AV, CF-C, TSho, Nka, NH, NJ, TG, MG, KZ, JS, LK, AKu, LBC, PH, US, SJ, PJJ, JMK, M-LCvV, DDB, SG, REM, ESL, LM, JRL, JBR, RV, MKC, RCT, LBC, CCF, JP, XF, KMM, PAN, MK, DTWJ, EL-A, DJHS, JAC, AN, EGVM, JJO, AJa, NG, WAW, DJM, CEH, UT, AKo, SMP, RJP, and MDT collected data. VR, S-KK, JYL, AANR, CG, KKWL, H-KN, TK, WAG, MP-P, SP, Y-JC, JM, IFP, RLH, SL, WJI, ARH, AJo, MF-M, AV, CF-C, TSho, Nki, NH, NJ, TG, MG, KZ, JS, LK, AKI, LBC, PH, US, SJ, PJJ, JMK, M-LCvV, DDB, SG, REM, ESL, LM, JRL, JBR, RV, MKC, RCT, CCF, JP, XF, KMM, PAN, MK, DTWJ, EL-A, JAC, AANR, EGVM, JJO, NG, WAW, DJM, CEH, UT, AKu, PD, JTR, AKo, SMP, RJP, and MDT provided materials. All authors analysed and interpreted the data. THi did the statistical analyses. EMT, THi, VR, EB, MR, DDB, PD, AKo, RJP, and MDT wrote the manuscript. All authors approved the final report.

Declaration of interests

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References

- 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**: 265–71.
- 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**: 832–45.

- 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**: 813–20.
- 4 Ramaswamy V, Northcott PA, Taylor MD. FISH and chips: the recipe for improved prognostication and outcomes for children with medulloblastoma. *Cancer Genet* 2011; **204**: 577–88.
- 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**: 4202–08.
- 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**: e33415.
- 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**: 4961–68.
- 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**: 480–87.
- 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**: 51–56.
- 10 Akyüz C, Varan A, Küpeli S, et al. Medulloblastoma in children: a 32-year experience from a single institution. *J Neurooncol* 2008; **90**: 99–103.
- 11 Evans AE, Jenkin RD, Spoto 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**: 572–82.
- 12 Stavrou T, Bromley CM, Nicholson HS, et al. Prognostic factors and secondary malignancies in childhood medulloblastoma. *J Pediatr Hematol Oncol* 2001; **23**: 431–36.
- 13 Grill J, Sainte-Rose C, Jouveta A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. *Lancet Oncol* 2005; **6**: 573–80.
- 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**: 464–69.
- 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**: 2936–41.
- 16 Albright AL, Spoto R, Holmes E, et al. Correlation of neurosurgical subspecialization with outcomes in children with malignant brain tumors. *Neurosurgery* 2000; **47**: 879–85.
- 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**: 19–29.
- 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**: 106–12.
- 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.
- 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* 2000; **123**: 1041–50.
- 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**: 182–87.
- 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**: 885–93.
- 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 Neuropathol* 2012; **123**: 473–84.
- 24 Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* 2012; **123**: 465–72.
- 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**: 1924–31.
- 26 Ramaswamy V, Remke M, Shih D, et al. Duration of the pre-diagnostic interval in medulloblastoma is subgroup dependent. *Pediatr Blood Cancer* 2014; **61**: 1190–94.
- 27 Northcott PA, Jones DT, Kool M, et al. Medulloblastomics: the end of the beginning. *Nat Rev Cancer* 2012; **12**: 818–34.
- 28 Northcott PA, Dubuc AM, Pfister S, Taylor MD. Molecular subgroups of medulloblastoma. *Expert Rev Neurother* 2012; **12**: 871–84.
- 29 Northcott PA, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. *Nat Rev Neurol* 2012; **8**: 340–51.
- 30 Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. *J Clin Oncol* 2011; **29**: 1408–14.
- 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**: 373–84.
- 32 Shih DJ, Northcott PA, Remke M, et al. Cytogenetic prognostication within medulloblastoma subgroups. *J Clin Oncol* 2014; **32**: 886–96.
- 33 Northcott PA, Shih DJ, Remke M, et al. Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. *Acta Neuropathol* 2012; **123**: 615–26.
- 34 Ramaswamy V, Remke M, Bouffet E, et al. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. *Lancet Oncol* 2013; **14**: 1200–07.
- 35 Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Heidelberg: 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 Neuropathol* 2014; **128**: 137–49.
- 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; published online Jan 20. DOI:10.1093/neuonc/nou357.
- 38 Perreault S, Ramaswamy V, Achrol AS, et al. MRI surrogates for molecular subgroups of medulloblastoma. *AJNR Am J Neuroradiol* 2014; **35**: 1263–69.
- 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**: 3187–93.
- 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; **32**: 1760–68.
- 41 Garrè ML, Cama A, Bagnasco F, et al. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome—a new clinical perspective. *Clin Cancer Res* 2009; **15**: 2463–71.