Table 9 Changes in child-reported HRQOL score based on method of administration ($N = 134$)

	Direct effect		Indirect effect			
	D	95% CI	*I*	95% CI	I1	I2
Cognitive problems	−6.4	(−12.0, −0.8)	−2.5	(−7.5, 2.5)	−0.14	18.1
Pain and hurt	−7.9	(−13.8, −1.9)	−1.3	(−3.8, 1.3)	−0.14	9.2
Movement and balance	−12.6	(−19.3, −6.0)	−2.5	(−7.6, 2.6)	−0.14	18.3
Procedural anxiety	−8.8	(−19.4, 1.8)	−1.1	(−3.5, 1.3)	−0.14	8.1
Nausea	−2.6	(−9.8, 4.6)	−1.1	(−3.5, 1.2)	−0.14	8.2
Worry	−0.6	(−8.0, 6.8)	−2.1	(−6.4, 2.2)	−0.14	15.3

CI confidence interval, *HRQOL* health-related quality of life, *D* path coefficients from the method of administration to child-reported HRQOL, *I* indirect effect from the method of administration to child-reported HRQOL, *I1* path coefficients from the method of administration to children's perception, *I2* path coefficients from the children's perception to child-reported HRQOL

own psychological distress and academic background. Interestingly, children's HRQOL scores from self- and interviewer-administered reports were comparable, showing that the results from bivariate and multivariate analyses were not biased by the method of administration. This important result suggests interviewer measurement of HRQOL for children who are unable to self-administer the questionnaire is valid.

The correlation coefficient between the method of administration and tendency for children to score their own HRQOL highly was −0.06 (95% CI −0.23 to 0.11). Given that correlation coefficients >0.1 are regarded as small, >0.3 as medium and >0.5 as large [37], this finding suggests that the method of questionnaire administration has only a small effect on the assessment of children's perception.

All scales of PedsQL™ were scored from 0 to 100, and the actual difference in child-reported score resulting from administration method ranged from −2.5 to −1.1 points. The US Department of Health suggests methods for inferring minimum clinically significant difference (MID) [38]. Using an empirical rule (e.g., 8% of the theoretical range of scores), the MID in a PedsQL™ score is 8 points. Using a distribution-based approach (e.g., defining the MID as 0.5 times the standard deviation), the MID in the PedsQL™ Brain Tumor Module scores reported a range from 9.2 to 17.2 points [24]. Other authors used a standard error of measurement approach to determine the MID for the PedsQL™ Generic Core Scales child-report was 4.4 [39]. Taken together, these previous findings suggest that the difference in child-reported score resulting from administration method in the present study, while not negligible, is not comparatively significant. As such, we feel confident in adopting an administration method for monitoring HRQOL in clinical settings best adapted to the environment.

Similarly, results for previous comparisons of administration methods show small differences albeit in opposing directions. Huguet and Miro, using a Catalan version of PedsQL™, reported that interviewer-administered scores were 2 points higher than self-administered scores [40]. In their assessment of very low birth weight children aged 14 years by the TACQOL, Verrips et al. [41] found that the interviewer-administered scores were 2 points lower than the self-administered score, whereas Tsakos et al. [42] found no significant difference between self- and interviewer-administered scores for oral HRQOL. Taken together, the findings from the present and previous studies suggest little difference between self- and interviewer-administered scores for child-reporting. Differences between findings for these present and previous studies may be due to differing criteria for HRQOL measured or differences in the children's diseases. To our knowledge, our present study is the first to report that the scores of self- and interviewer-administered questionnaires for HRQOL in children with brain tumors using PedsQL™ are comparable.

Consistent with results for other children with cancer [14], we also found that trait anxiety alters children's own perception about HRQOL. As trait anxiety has a greater effect than the other factors, it should be considered in the interpretation of child-reported scores. Given that trait anxiety is one personality characteristic that does not vary substantially over time [28], if self-reported scores from repeated measurements of a child with a brain tumor are consistently lower than parent-reported scores, the measured result may be attributed to high trait anxiety of the child.

The effect of treatment status on a parent's perception about their child's HRQOL has not been previously investigated. Parents of children on treatment tended to have a lower perception about their child's HRQOL than those of children off treatment, whereas treatment status had no influence on children's perception. As a result, clinical practice or research should use both child- and parent-reports whenever possible, particularly when

HRQOL questionnaires are needed to assess HRQOL variations during the course of treatment, changes in environment, or psychosocial intervention. For example, HRQOL reports from parents and children changed at 1, 6, and 12 months after diagnosis of brain tumor [19]. The pattern of child-reported HRQOL was different from parent-reported HRQOL over time indicating the importance of using use both child- and parent-reports.

Parents may feel a stronger impact of their child's illness than the child himself or herself [43]. In previous studies, parent-reported HRQOL scores were higher than child-reported scores for children without health problems and lower than child-reported scores for children with health problems. Our study also suggests that parents are more aware of their child's treatment through knowledge of tumor symptoms and treatment pain. In other words, the parents may feel a stronger impact of their child's treatment than the child himself or herself and accordingly tend to score the HRQOL of these children lower than the parents of children off treatment.

Vance et al. [44] suggested that parent-reported HRQOL was not influenced by parent's depression. The present study, however, which had a larger sample size than previous studies, found that the parent-reported HRQOL was affected by the parent's own psychological distress. This suggests that the parent's own prospects and cognitive tendency influence their perception about their child's HRQOL.

The present study is the first to use an MTMM model to identify factors that influence child or parent perception about HRQOL. This knowledge will be useful in interpreting the discordance between child- and parent-reports of HRQOL in children with brain tumors. In clinical settings, this finding will allow clinicians to take high trait anxiety in the child or high psychological distress in the parent into account. For example, when the child is off treatment, it will be less surprising that child-reported HRQOL score is low and parent-reported HRQOL score is high if the child has low trait anxiety. Routine measurements in clinical settings thus have the potential to allow the monitoring of both the child's personality and the mental state of his/her parents. This finding will also improve the selection of children for comparison of HRQOL among multiple groups. For example, in non-randomized controlled trials, children may be allocated among groups with consideration to equality of anxiety in children and mental health in parents. Our findings also suggest that single group studies should collect information on parents' academic background as well as other demographic characteristics, such as gender, age, race, etc., that influence selection bias.

Several limitations to our study warrant mention. First, as a cross-sectional study, changes in perception over time were not tested. Accordingly, we cannot conclude that the perception of a parent or child with a brain tumor will change at the end of treatment. Clarification of intrapersonal change in perception or response shift of children with brain tumors and their parents will require a longitudinal study.

Second, we did not conduct an a priori sample size calculation because this study is a part of another study [24] that has a predetermined sample size. The effect of sample size was calculated by G*Power software [45]. If a characteristic that has a medium effect ($f^2 \geq 0.15$ [37]) on either children's or parents' perception is added to a multiple linear regression model with 3 variables, a sample of 55 would enable detection of the characteristic as the 4th independent variable with 80% power and a 5% alpha error. Similarly, a sample of 395 would be required to detect a characteristic that has a small effect ($f^2 \geq 0.02$ [37]) as the 4th independent variable. It follows that the sample size of the present study was sufficient to detect factors having a medium effect. A larger sample might discriminate additional characteristics that were not found to be statistically significant in the present study, such as children's age and economic status.

A larger sample size would also enable simultaneous modeling of responses (MTMM model, Fig. 3) and predictors (predictor model, Tables 4, 6, and Fig. 1), which might then detect any correlation between the predictors and the latent variables of rater-independent assessments of the child's condition. Further, a larger sample size should enable researchers to detect the effect of interviewer type (e.g., parent or researcher interviewer) on a child's perception. Among children aged five-to-seven and eight or more years, those interviewed by a parent tended to have a lower perception about HRQOL than those interviewed by a researcher, although this result was not statistically significant.

Third, we were unable to measure all possible factors that might influence child-parent agreement. We limited the length of our questionnaires to avoid placing further stress on the children, and therefore, measurements of the child's psychological background were limited to anxiety. Other aspects of a child's personality, such as defensiveness [14], might also influence the results, and future research should therefore investigate different personality traits. We also omitted measurements of the child's physical background, such as tumor location, tumor malignancy, relapse history, or treatment intensity [18–22]. All data in the present study were collected not from medical experts but from the children and their parents; as such, obtaining accurate, detailed answers about medical information was somewhat difficult. Additional information derived from patients with specific tumors or under specific treatment regimens will be required to identify residual confounders.

An additional constraint arises from the sample type. The present study collected data from a broad spectrum of children who had experienced brain tumors and included, for example, children diagnosed from 1 month to 17 years before the study. We could cover the broad spectrum to make up the study sample of the two subsamples. The hospitals subsample included more children with short time since diagnosis, young at survey, and on treatment than the CCAJ subsample did. To provide further insight into self- or parent-perceptions about HRQOL, further studies should focus on children at different phases of treatment or follow-up.

Families were excluded if the doctors or social workers determined that the family found the subject of the child's condition too uncomfortable to discuss. Although the number of such excluded families was not recorded, this exclusion may have limited data collection to more well-adjusted families and thereby limited the generalizability of the conclusions as well.

Finally, independent variables identified in this study accounted for 26.4% of the children's perception and 17.3% of the parents' perception. Other independent factors were not identified.

Conclusion

The method of administration—self- or interviewer-administered—had little influence on child-reporting of HRQOL. Children's perception of their own HRQOL was influenced by their trait anxiety, while parents' perception was influenced by their psychological distress, academic background, and their child's treatment status. These factors underlie the difference between child- and parent-reported HRQOL scores.

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Subgroup-Specific Prognostic Implications of *TP53* Mutation in Medulloblastoma

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ABSTRACT

Purpose
Reports detailing the prognostic impact of *TP53* mutations in medulloblastoma offer conflicting conclusions. We resolve this issue through the inclusion of molecular subgroup profiles.

Patients and Methods
We determined subgroup affiliation, *TP53* mutation status, and clinical outcome in a discovery cohort of 397 medulloblastomas. We subsequently validated our results on an independent cohort of 156 medulloblastomas.

Results
TP53 mutations are enriched in wingless (WNT; 16%) and sonic hedgehog (SHH; 21%) medulloblastomas and are virtually absent in subgroups 3 and 4 tumors ($P < .001$). Patients with SHH/*TP53* mutant tumors are almost exclusively between ages 5 and 18 years, dramatically different from the general SHH distribution ($P < .001$). Children with SHH/*TP53* mutant tumors harbor 56% germline *TP53* mutations, which are not observed in children with WNT/*TP53* mutant tumors. Five-year overall survival (OS; ± SE) was 41% ± 9% and 81% ± 5% for patients with SHH medulloblastomas with and without *TP53* mutations, respectively ($P < .001$). Furthermore, *TP53* mutations accounted for 72% of deaths in children older than 5 years with SHH medulloblastomas. In contrast, 5-year OS rates were 90% ± 9% and 97% ± 3% for patients with WNT tumors with and without *TP53* mutations ($P = .21$). Multivariate analysis revealed that *TP53* status was the most important risk factor for SHH medulloblastoma. Survival rates in the validation cohort mimicked the discovery results, revealing that poor survival of *TP53* mutations is restricted to patients with SHH medulloblastomas ($P = .012$) and not WNT tumors.

Conclusion
Subgroup-specific analysis reconciles prior conflicting publications and confirms that *TP53* mutations are enriched among SHH medulloblastomas, in which they portend poor outcome and account for a large proportion of treatment failures in these patients.

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INTRODUCTION

Medulloblastoma is a malignant small-cell embryonal neoplasm of the cerebellum. It is the most common malignant brain tumor of childhood and remains a major cause of morbidity and mortality in this age group. Currently, medulloblastomas are mostly stratified based on histologic and clinical and radiologic criteria, which include age of onset, metastatic spread, and residual tumor after surgery. Stratification and management according to clinical risk criteria and development of large cooperative clinical trials resulted in improved survival for these individuals.[1-3] However, aggressive multimodal treatment protocols carry high morbidity; thus differentiation between patients with favorable and poor outcomes would be highly desirable. The difficulty to predict tumor recurrence based on clinical

criteria only has resulted in recent extensive efforts using integrative genomics to allow for genetic and molecular stratification of the disease.[4-6] As of today, none of these molecular markers are routinely used in the clinic or as part of clinical trials. We have reported previously, using the Toronto cohort, that survival is dismal for children with medulloblastoma harboring *TP53* mutations.[7] Subsequently, a similar analysis of patients from the Heidelberg cohort did not confirm the unfavorable prognosis of *TP53*-mutated tumors.[8] Moreover, additional reports from English and German cohorts revealed uncertainty with regard to the role of *TP53* alterations in risk stratification of medulloblastoma.[9,10] Recently, several groups were able to demonstrate that although morphologically similar, medulloblastomas could be divided into several subgroups on the basis of expression profiling.[11-13] A consensus meeting resulted in the current molecular subclassification of medulloblastoma into four subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.[14] It is hoped that, in the near future, this subclassification will be used to select targeted therapies and improve understanding of the behavior of this disease. However, other than the WNT group, which is consistently associated with excellent survival,[15,16] SHH tumors, group 3 tumors, and group 4 tumors show heterogeneous outcomes. Recent meta-analysis revealed lack of significant difference in the overall survival (OS) between the latter three groups.[17] Because our group was recently able to demonstrate a unique association of certain genetic catastrophic events (chromothripsis) specifically in patients with SHH/*TP53* mutant medulloblastomas,[18] we hypothesized that this unique association might explain both the controversy regarding the prognostic role of *TP53* mutations in medulloblastoma and the heterogeneous outcome of patients with SHH medulloblastomas. We therefore compiled both clinical and molecular data from multiple centers to generate a large discovery cohort of patient and tumors with known *TP53* status. We then performed subgroup combined with outcome analysis for the first time (Appendix Table A1, online only). We then sequenced and characterized a second, large independent validation cohort from the Medulloblastoma Advanced Genomics International Consortium (MAGIC), for which high-quality clinical data and sufficient tissue were available, thereby allowing us to determine the association of *TP53* mutations, molecular groups, and survival in medulloblastoma.

PATIENTS AND METHODS

Patients

We assembled the clinical and biologic data of patients included in our previous studies for which subgroups have now been assigned, along with additional new samples from all centers (n = 397, Table 1). These included tumors and patient data from the Hospital for Sick Children (HSC) in Toronto, Canada, the Heidelberg database (DKFZ), and the British (Newcastle)[9] and German cohorts.[10] All patient samples were procured in accordance with the research ethics board of their corresponding institution. For 373 patients (92%), clinical and survival data were available for analysis. An independent validation cohort of SHH and WNT tumors with available outcome data and sufficient DNA for sequencing (n = 156) was obtained through MAGIC.[19] Further clinical and demographic data from both cohorts are detailed in Table 1. For progression and OS analysis, time was defined as months from initial diagnosis.

Samples from all centers were either obtained as frozen tissue or formalin-fixed paraffin-embedded biopsies, and nucleic acids from the frozen tissue were extracted as previously described.[19] Nucleic acids were extracted from frozen and formalin-fixed paraffin-embedded samples as previously described.[8]

Table 1. Patient Characteristics by *TP53* Mutational Status

	Discovery Cohort					Validation Cohort				
	TP53 Mutant		*TP53* Wild Type			*TP53* Mutant		*TP53* Wild Type		
Variable	No.	%	No.	%	*P*	No.	%	No.	%	*P*
No.	41		356			22		134		
Age, years										
Median	11.7		10.65			10.7		12.1		
Range	1-45		0-52			1.8-33		0-56		
Age < 3	2	4.9	60	16.8	.04	1	4.5	43	32.1	.009
Adults > 18	4	9.8	60	16.9	.4	4	18.2	30	22.4	.8
Male sex	18	43.9	213	60	.07	10	47.6	73	55.3	.7
Histology					< .001					.002
LCA	17	42.5	43	12.3		8	44.4	14	10.7	
Classic	22	55.0	254	72.8		8	44.4	68	59.8	
Desmoplastic	1	2.5	52	14.9		2	11.1	33	29.5	
M+ disease	4	10.5	110	31.9	.005	5	25	21	18.3	.5
Recurrence	24	58.5	114	32.0	.003	NA		NA		
Dead	18	43.9	82	23.0	.011	9	40.9	27	20.1	.03
Subgroup					< .001					.28
WNT	11	26.8	55	15.4		7	31.8	28	20.9	
SHH	28	68.3	105	29.5		15	68.2	106	79.1	
Group 3	0		72	20.3						
Group 4	1	2.4	121	34						
Missing	1		3	0.8						

NOTE. Histology was available for 389 cases in the discovery and 130 cases in the validation cohorts. Metastatic status at diagnosis was available in 269 cases in the discovery and 135 cases in the validation cohorts.
Abbreviations: LCA, large cell/anaplastic; NA, not applicable; SHH, sonic hedgehog; WNT, wingless.

Subgroup Analysis

Molecular subgrouping was performed on the HSC screening and the MAGIC validation cohort using a custom nanoString codeset designed to assess the expression of 22 medulloblastoma subgroup-specific signature genes as previously described.[20] Samples were processed at the University Health Network (UHN) Microarray Facility using an input of 100 ng of total RNA. Subgrouping of the DKFZ samples were determined by gene expression profiling or by immunohistochemistry and nanoString codeset as previously described.[8,21,22] Subgrouping of the Newcastle samples was determined by a limited gene expression signature as previously described.[13]

TP53 Mutation Analysis

TP53 sequencing for the HSC and validation cohorts was performed on the entire coding sequence (exons 2 through 11) with primers and methodology as previously described.[23,24] *TP53* sequencing for the Heidelberg and the Newcastle cohort was performed as previously described.[8,9] For patients with *TP53* mutant tumors when blood DNA was available, germline mutation status was assessed to determine the diagnosis of Li-Fraumeni syndrome (LFS).[25]

Statistical Analysis

Statistical analysis was performed in the R statistical environment (v2.15). Univariate survival analysis was performed using the log-rank test as implemented in the survival R package (v2.36). Multivariate Cox proportional hazards regression was used to adjust for additional covariates using the survival R package (v.2.36). In all cases, $P < .05$ was considered significant. Stabilities of prognostic markers were assessed by bootstrap resampling as previously described,[26] using the Akaike information criterion for variable selection by backward elimination in 1,000 bootstrap replicates. For correlative studies, the Fisher's exact test was used.

RESULTS

Characteristics of TP53 Mutated Medulloblastomas

In the discovery cohort, we identified *TP53* mutations in 41 (10%) of 397 medulloblastomas. Median age at diagnosis for patients with *TP53* mutant tumors was 11.7 years (range, 1.1 to 45 years). The male to female ratio was 1:1.2. Only 10.5% of *TP53* mutant tumors were metastatic at diagnosis (Table 1). Diffuse anaplasia was observed in 42.5% of mutant tumors. Only one tumor had a concomitant *MYCC* amplification, whereas eight tumors demonstrated simultaneous *MYCN* amplification. Interestingly, of these nine patients, six are alive with a mean follow-up of 4.5 years. At a median follow-up of 49 months (range, 3 to 226 months), 5-year OS for all patients in the discovery cohort was 77% ± 6% and 55% ± 8% for *TP53* wild-type and mutant medulloblastomas, respectively ($P < .001$; Fig 1A).

TP53 Mutational Pattern by Subgroup

TP53 mutations were found predominantly in the SHH and WNT groups. Specifically, *TP53* mutations were observed in 11 (16%) of 66 WNT and 28 (21%) of 133 SHH tumors. In contrast, *TP53* mutations were observed in only one of 122 group 4 and in 0 of 72 group 3 tumors (Fig 2A; $P < .001$). The age distribution observed in patients with SHH/*TP53* mutant medulloblastoma revealed a Gaussian curve peaking at approximately age 15 years, whereas a bimodal age distribution was observed in SHH/*TP53* wild-type tumors (Fig 2B). Most of the patients with SHH/*TP53* mutant tumors (25 of 28) were between the ages of 5 and 18 years, which differs dramatically from SHH/*TP53* wild-type ones (31 of 105; $P < .001$). None of the WNT/*TP53* mutant tumors demonstrated anaplastic features, whereas 68% of SHH/*TP53* mutant tumors had severe anaplasia ($P < .001$). Similarly, none of the WNT/*TP53* mutant tumors harbored *MYC* or *MYCN* amplifications, whereas 33% of SHH/*TP53* mutant tumors exhibited these genetic alterations ($P = .05$). *TP53* mutations were observed in the DNA-binding domain (exons 4 through 8; Fig 2C). The most common mutations were in codons 248 and 175, which are the most commonly mutated residues in both somatic and germline *TP53* mutation databases (International Agency for Research on Cancer).[26a] Of the patients for whom *TP53* germline status was available (n = 20), nine patients (45%) harbored germline mutations consistent with LFS. All these individuals had SHH tumors. Although 56% of SHH/*TP53* mutant tumors had a concomitant germline mutation, germline mutations were not seen in WNT/*TP53* mutant tumors.

TP53 Mutations and Survival by Subgroup

A striking association between biologic subgroups and survival for patients with *TP53* mutant tumors was observed. Specifically, patients with SHH/*TP53* mutant tumors had 5-year OS of 41% ± 19%, whereas patients with WNT/*TP53* mutant tumors had 5-year OS of 90% ± 9% ($P = .018$; Fig 1B). Five-year OS was 41% ± 9% and 81% ± 5% for patients with SHH tumors with and without *TP53* mutations ($P < .001$; Fig 1C). However, for children between the ages of 5 and 18 years with SHH tumors, *TP53* mutations accounted for 72% of deaths. Within the limitations of a small cohort, children with confirmed LFS had survival similar to that of the remaining patients with *TP53* mutant SHH medulloblastomas (Appendix Fig A1, online only). In contrast, 5-year OS was 90% ± 9% and 97% ± 3% for patients with WNT tumors with and without *TP53* mutations ($P = .21$; Fig 1D). A multivariate Cox proportional hazards regression model of 5-year survival for SHH tumors accounting for age, sex, histology, presence of metastases, and *TP53* status demonstrated that *TP53* mutation status is the single most important independent risk factor for this group (Table 2).

Validation of Survival Analysis for SHH and WNT Tumors

To validate the survival difference between WNT and SHH *TP53* mutant medulloblastomas observed in our new assembled cohort, we performed additional Sanger sequencing of *TP53* in a separate cohort of 156 patients with medulloblastoma from the SHH and WNT groups with adequate clinical data, who were available through MAGIC. The rate of *TP53* mutations in this cohort was similar to the rate seen by our group. Most patients (81%) had nonmetastatic tumors, and the male to female and age distributions were similar to those of our initial cohort. Diffuse anaplasia was reported in 54% of SHH/*TP53* mutant tumors and 12% of SHH/*TP53* wild-type ones ($P = .002$). None of the WNT/*TP53* mutant tumors were defined as anaplastic. The OS of this cohort mimicked the observed findings in our initial cohort (Figs 2E and 2F). At a median follow-up of 42 months (range, 2 to 300 months), 5-year OS for patients with SHH tumors with and without *TP53* mutations was 41% ± 17% and 76% ± 4%, respectively ($P = .012$); in contrast, 5-year OS for patients with WNT tumors with and without *TP53* mutations was 86% ± 13% and 94% ± 5%, respectively ($P = .41$).

Additional Data From All Patients in the Study

Summarizing all data from all patients from whom all clinical and molecular data were available enabled us to further clarify several observations. Combining all patients with SHH medulloblastomas

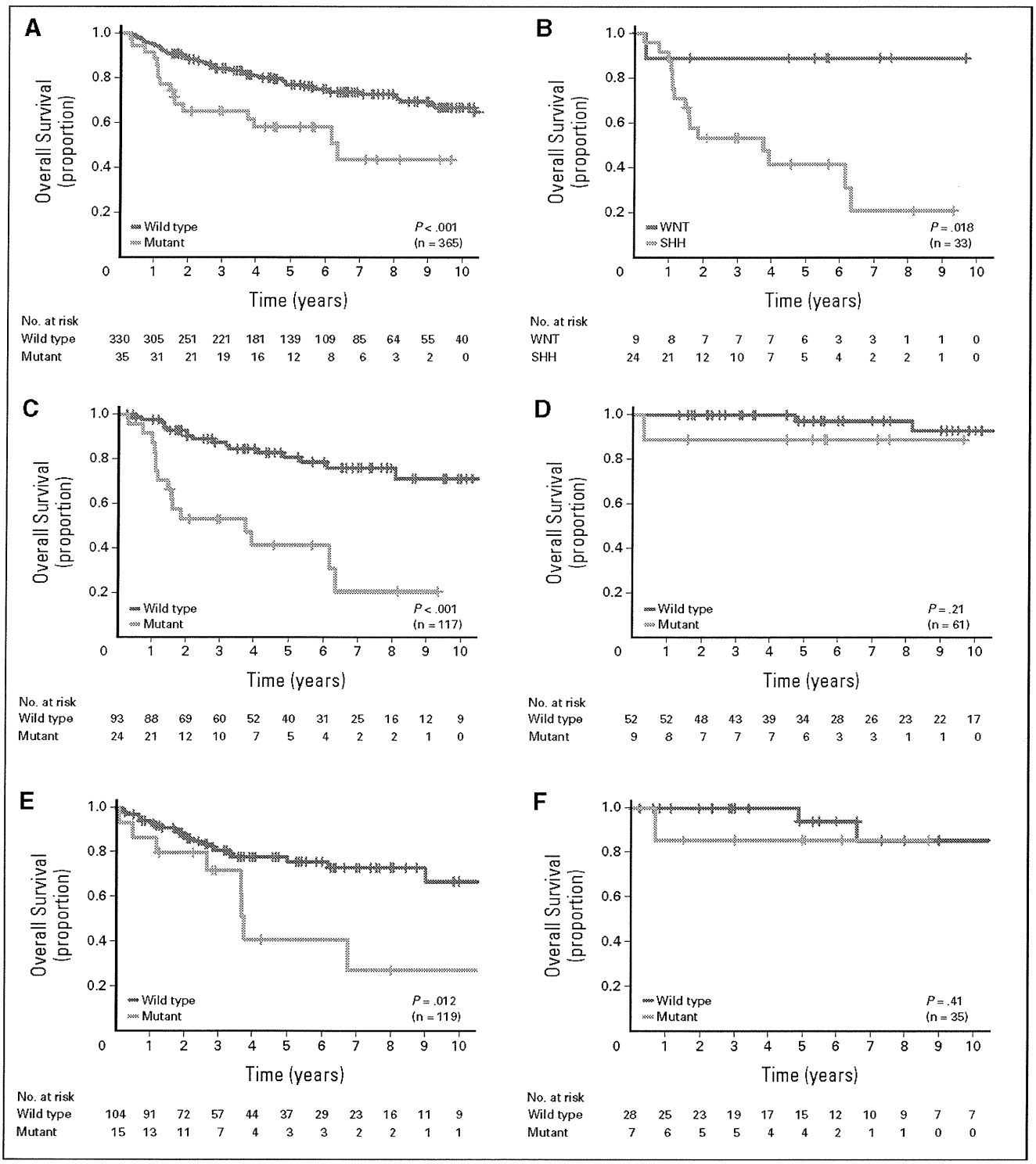

Fig 1. Kaplan-Meier estimates of overall survival for study patients by group. (A) All discovery cohort patients by *TP53* mutations. Blue line, *TP53* wild type, wingless (WNT) group; gold line *TP53* mutant, sonic hedgehog (SHH) group. (B) *TP53*-mutant tumors stratified by subgroup analysis. Blue line, WNT group; gold line, SHH group. (C) Blue line, *TP53* wild type, WNT group; gold line, *TP53* mutant, SHH group. (D) WNT tumors from the discovery cohort. Blue line, *TP53* wild type, WNT group; gold line, *TP53* mutant, SHH group. (E) SHH tumors from the validation cohort. Blue line, *TP53* wild type, WNT group; gold line, *TP53* mutant, SHH group. (F) WNT tumors from the validation cohort. Blue line, *TP53* wild type, WNT group; gold line, *TP53* mutant, SHH group.

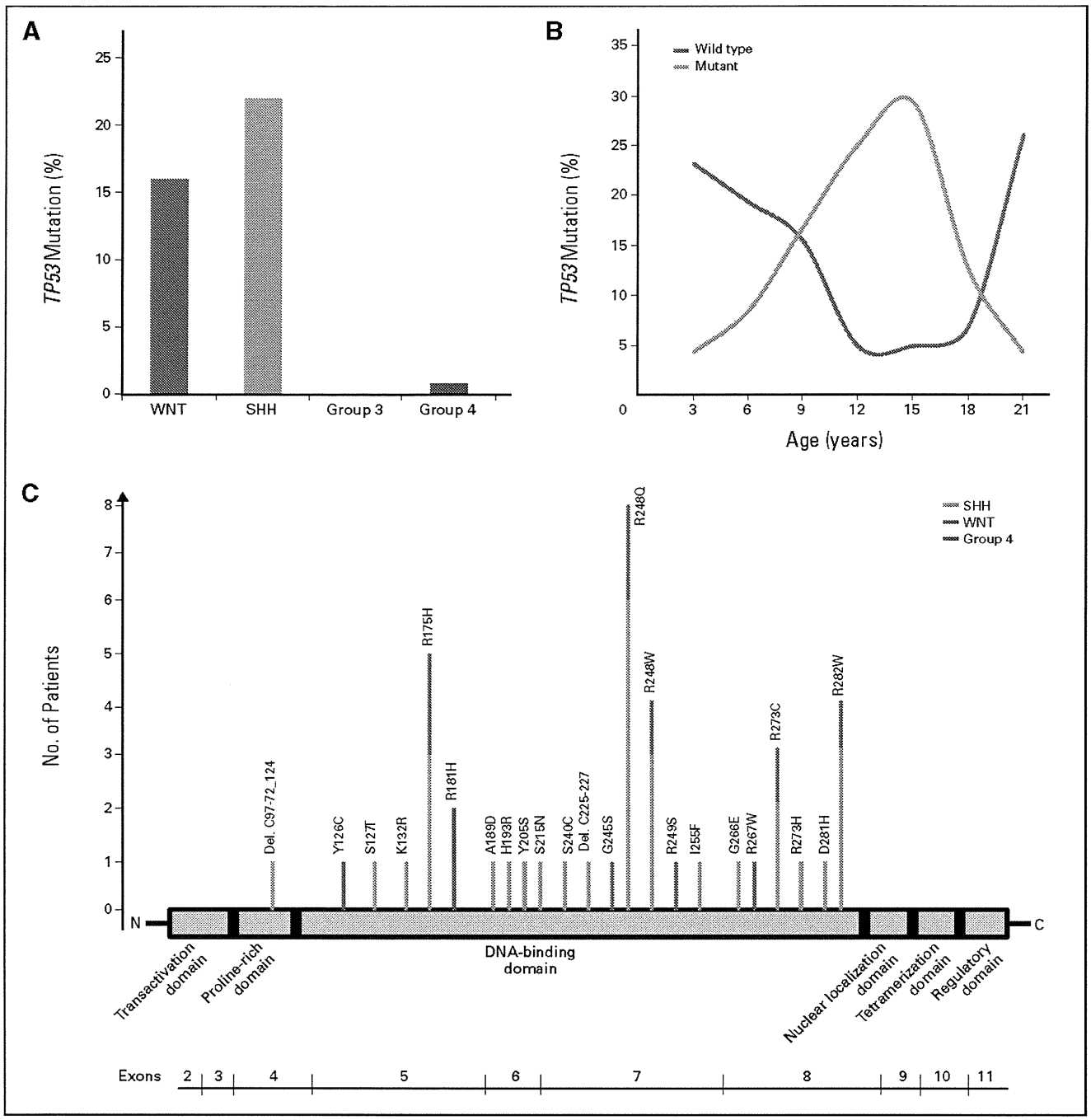

Fig 2. Characteristics of *TP53* mutation in medulloblastoma. (A) Percentage of *TP53* mutations in medulloblastoma subgroups; (B) Age distribution of sonic hedgehog (SHH) medullablastoma according to *TP53* status. (C) Distribution of *TP53* mutations according to functional domains. WNT, wingless.

between the ages of 5 and 18 years (where radiation is usually given to all children, n = 84) revealed that tumors carrying *TP53* mutations were associated with 21 (72%) of 29 deaths ($P < .001$; Appendix Fig A2, online only). The combined cohorts included 42 adults, of whom six (14%) had *TP53* mutant tumors. Five of these patients died of their disease. Interestingly, two patients had WNT tumors, and none survived.

DISCUSSION

The genetic and genomic understanding of medulloblastoma has evolved dramatically in the past few years. International collaborations have resulted in novel classification of this brain tumor and the potential for targeted therapies for patients within specific subgroups.

Table 2. Multivariate Cox Proportional Hazards Regression Models of Overall Survival in SHH Subgroup Medulloblastoma

Variable	Hazard Ratio	95% CI	BIF	*P*
Discovery cohort				
TP53 mutation	4.39	1.70 to 11.29	95.7	.002
LCA *v* classic	1.07	0.39 to 2.90	20.9	.90
Desmoplastic *v* classic	0.45	0.17 to 1.22	54.0	.11
Sex (male *v* female)	1.21	0.56 to 2.58	24.3	.63
M+	0.38	0.11 to 1.37	58.6	.14
Age < 3 years	1.41	0.51 to 3.87	25.1	.51
Validation cohort				
TP53 mutation	14.7	3.44 to 62.9	97.6	< .001
LCA *v* classic	2.90	0.79 to 10.6	47.1	.11
Desmoplastic *v* classic	0.41	0.08 to 2.14	43.9	.29
Sex (male *v* female)	0.71	0.24 to 2.11	24.4	.54
M+	26.4	5.96 to 117.5	99.4	< .001
Age < 3 years	4.15	0.93 to 18.6	60.7	.062

Abbreviations: BIF, bootstrap inclusion frequency; LCA, large cell/anaplastic; SHH, sonic hedgehog.

Nevertheless, except for patients with WNT tumors, for whom outcome is superior to all other subgroups, survival of children with SHH, group 3, and group 4 tumors is still unsatisfactory.[17]

In this study, we demonstrate that characterization of *TP53* mutation status can segregate individuals with SHH medulloblastoma into favorable and extremely poor survival groups. Specifically, patients with SHH/*TP53* mutant medulloblastomas have profoundly worse outcome than those with SHH/*TP53* wild-type tumors. The importance of this observation is further highlighted by the fact that most patients with *TP53* mutant medulloblastomas have average-risk tumors, as measured by conventional nonmolecular methods, for which survival is expected to be excellent with current protocols.[1,2] To validate our observations from the discovery cohort, we examined a separately ascertained cohort that included a large number of children and adults with SHH and WNT tumors. The impressive similarity in outcomes between the two cohorts argues against an unobserved variable confounding the results of our discovery cohort. Moreover, large whole-genome and exome sequencing efforts recently published by separate groups revealed an additional, albeit small number, of *TP53* mutations in medulloblastoma.[27-29] Interestingly, these independent groups found *TP53* mutations enriched in the SHH group and associated with poor survival. In fact, of 14 SHH tumors studied by Robinson et al,[29] deaths were only reported in the three *TP53* mutant tumors. The observation that a significant number of deaths in the SHH cohort were associated with *TP53* mutations in both our and other cohorts suggests that somatic *TP53* mutations analysis should be performed on patients with SHH medulloblastomas (Fig 3).

Our study also highlights how genomic and molecular stratification could explain differences in clinical and biologic behavior of cancers with a specific genetic alteration. Indeed, although patients with SHH *TP53* mutated tumors fared miserably, this aggressive genotype was completely modified in WNT tumors. Our group has recently shown that WNT activation through constitutive β-catenin activation can abrogate the radioresistance conferred by *TP53*-mutated medulloblastomas as a potential explanation for this difference in outcome.[30] The separation of SHH subgroup patients by *TP53* status would significantly improve risk stratification of this subgroup, analogous to the role of *FSTL5* in stratifying group 3 and 4 patients.[22] Indeed, our multivariate modeling would suggest that a simple model

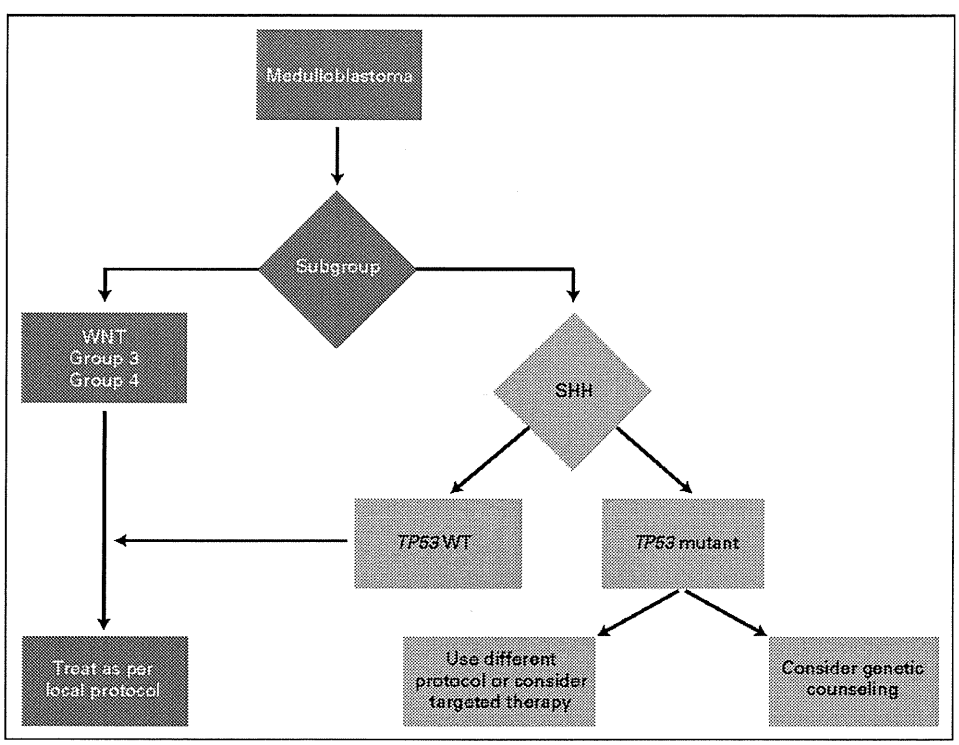

Fig 3. Risk stratification for patients with medulloblastoma based on molecular subgroups and *TP53* status. SHH, sonic hedgehog; WNT, wingless; WT, wild type.

of subgroup along with *TP53* mutation status is highly predictive of outcome.[31]

SHH/*TP53* mutant medulloblastomas have several biologic characteristics that can explain their clinical behavior. These tumors reveal a high rate of *MYCN* amplification. Furthermore, our group was recently able to demonstrate that these cancers have a high rate of single chromosomal shattering, or chromothripsis.[18] This catastrophic event is associated with poor survival and a high degree of genomic instability in other cancers[31-33] and therefore offers a plausible explanation for the poor survival of these patients.

The primary aim of this study was to assess somatic *TP53* alterations in medulloblastoma. However, our germline data from a subgroup of these patients demonstrate a high rate of germline *TP53* mutations. These findings have important implications to both the patient and other family members in terms of their subsequent cancer risk. Individuals with LFS, which is a devastating cancer predisposition syndrome, were recently shown to derive benefit from a clinical surveillance protocol.[34] Therefore, genetic counseling should be offered to all patients and families with SHH *TP53* mutant medulloblastomas.

Although our WNT *TP53* mutant tumors had a poor outcome among adults, the data are based on a small number of tumors, albeit suggesting that adults might deserve a different approach then children regarding genetic and molecular stratification.[35]

Although the effects of *TP53* mutation were different in SHH and WNT subgroups, the interactions between *TP53* mutation and subgroup (SHH *v* WNT) was not statistically significant in the discovery ($P = .62$) and validation cohorts ($P = .70$). Our data are consistent with the proposition that patients with mutant *TP53* WNT tumors do not have poorer survival compared with their wild-type counterpart, although the alternative possibility cannot be ruled out because of the rarity of *TP53* mutation in patients with WNT tumors. In this study and others,[36] *TP53* mutations were highly associated with anaplasia. In our study, anaplasia was seen in 19 (66%) of 29 SHH *TP53* mutant tumors and only in 14 (10%) of 136 SHH *TP53* wild-type ones ($P < .001$). This suggests that high index of suspicion for *TP53* mutations should exist for SHH tumors with diffuse anaplasia.

Finally, we suggest a clinicopathologic approach to medulloblastoma based on molecular subgroups and *TP53* status (Fig 3). In institutions where molecular group stratification is available, determination of molecular subgroup should be performed. Although some centers use RNA-based assays that may be difficult to reproduce by all institutions, efforts are being made to optimize antibody-based assays,[14,22] which aim to define SHH tumors in a robust and simple way for most clinical laboratories.[37] SHH subgroup tumors should be sent for *TP53* sequencing by clinically approved laboratories. For most institutions where molecular subgroups are not available, determination of *TP53* status should be performed in conjunction with nuclear β-catenin status. *TP53* mutational analysis is preferably done by direct sequencing. However, p53 immunostaining is a very sensitive (albeit not specific) surrogate method for *TP53* mutation detection in brain (and other) tumors and could be performed as an initial screening tool.[7,38,39] In our previous cohort, all *TP53* mutant tumors were immunopositive.[7] In this cohort and in our larger pediatric brain tumor cohort, immunostaining is more than 90% sensitive for detection of *TP53* mutations, and false negatives are generally restricted to deletions and splice site mutations in which no or truncated protein is expressed.[7,39,40] Tumors harboring *TP53* mutations should be then sent for subgroup analysis for determination of SHH status. Because current treatment protocols for patients with average-risk medulloblastoma result in dismal survival for those with *TP53* mutant SHH medulloblastomas, these patients should be considered for either enrollment in clinical trials of targeted therapy and/or other modified therapies. Furthermore, careful history of prior cancers in the family and genetic counseling should be offered to these individuals because of the high rate of LFS in this population. This practical approach can be also used in future clinical trials that are trying to stratify patients for reduced therapy.

In summary, this study serves as a proof of principle that collaborative efforts can resolve discrepancies between reports of an uncommon event in cancer. Specifically, this approach validated the prognostic role of *TP53* mutations in medulloblastoma once molecular subgroup is taken into account. This study also adds another dimension to the evolving role of genomic and genetic approaches to cancer by demonstrating that SHH-driven medulloblastomas, which account for a third of medulloblastomas seen in children, should be stratified according to their *TP53* status, whereas *TP53* mutation status has little prognostic effect in the setting of a WNT medulloblastoma. Ongoing collaborations between centers will allow for elucidation of the role of *TP53* alterations in adult medulloblastomas as well as the design of rational therapies for children with medulloblastoma in an era of precision medicine.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Patient Distribution According to Subgroups and *TP53* Status (discovery cohort)

	Newcastle		DKFZ		Sick Kids		Boston		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
WNT										
Wild type	13	65	35	11	7	11.7	0	0	55	13.9
Mutant	2	10	6	1.9	1	1.7	2	66.7	11	2.8
SHH										
Wild type	3	15	90	28.7	12	20	0	0	105	26.4
Mutant	1	5	18	13.3	8	13.3	1	33.3	28	7.1
Group 3										
Wild type	0	0	59	18.8	13	21.7	0	0	72	18.1
Mutant	0	0	0	0	0	0	0	0	0	0
Group 4										
Wild type	0	0	105	33.4	16	26.7	0	0	121	30.5
Mutant	0	0	1	0.3	0	0	0	0	1	0.3
Missing										
Wild type	0	0	0	0	3	5	0	0	3	0.8
Mutant	1	5	0	0	0	0	0	0	1	0.3
Total	20	100	314	100	60	100	3	100	397	100

Abbreviations: DKFZ, Heidelberg database; SHH, sonic hedgehog; WNT, wingless.

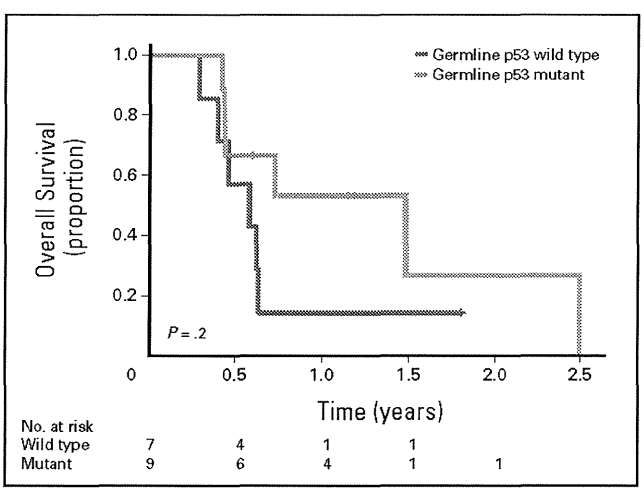

Fig A1. Survival estimates for children with sonic hedgehog (SHH)/*TP53*-mutant tumors when germline *TP53* status was available (n = 16).

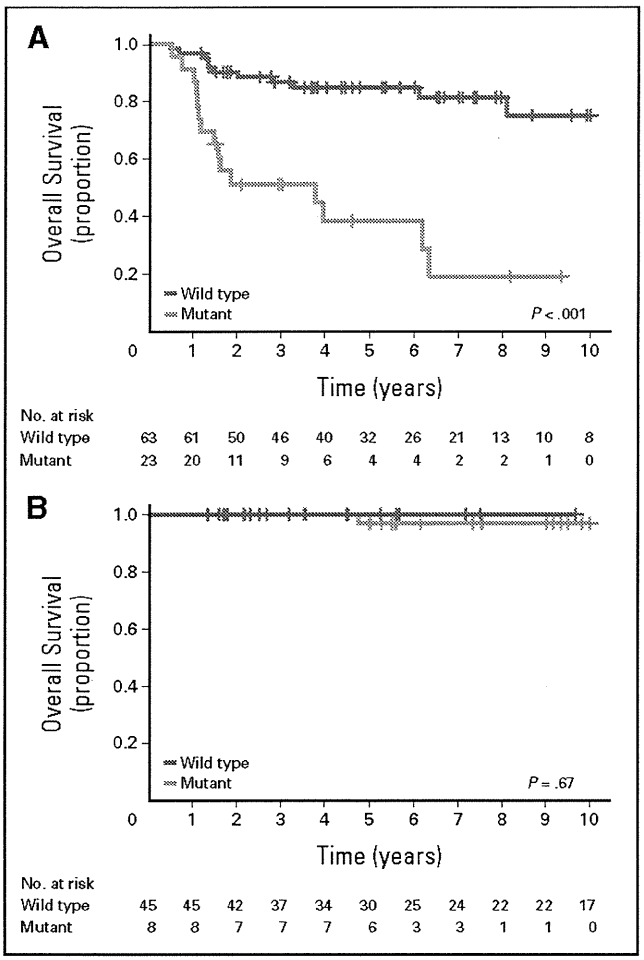

Fig A2. Kaplan-Meier estimates of overall survival for children and infants by group. (A) Sonic hedgehog (SHH) tumors from the discovery cohort. (B) Wingless (WNT) tumors from the discovery cohort.

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CLINICAL STUDY

Role of surgery, radiotherapy and chemotherapy in papillary tumors of the pineal region: a multicenter study

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Abstract Papillary tumor of the pineal region (PTPR), recently described as a distinct clinicopathological entity, can show aggressive biological behavior. The optimal therapeutic approach of PTPR has not been well defined. The role of surgery, radiotherapy, and chemotherapy in the treatment of PTPR was analyzed in a large multicenter series. In order to determine factors that influence prognosis, outcome data of a series of 44 patients with histopathologically proven PTPR were retrospectively analyzed. Of the 44 patients, 32 were still alive after a median follow-up of 63.1 months. Twelve patients experienced progressive disease, with seven undergoing two relapses and five more than two. Median overall survival (OS) was not achieved. Median progression-free survival (PFS) was 58.1 months. Only gross total resection and younger age were associated with a longer OS, radiotherapy and chemotherapy having no significant impact. PFS was not influenced by gross total resection. Radiotherapy and chemotherapy had no significant effect. This retrospective series confirms the high risk of recurrence in PTPR and emphasizes the importance of gross total resection. However, our data provide no evidence for a role of adjuvant radiotherapy or chemotherapy in the treatment of PTPR.

Keywords Papillary tumor of the pineal region · Pediatric · Prognosis · Radiosurgery

Introduction

Tumors located in the pineal gland region are rare neoplasms, constituting 0.5–1 % of all intracranial tumors [1],

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and comprise a variety of entities, including pineal parenchymal tumors, germ cell tumors, glial tumors, and meningiomas. Papillary tumor of the pineal region (PTPR) is a neuroectodermal tumor thought to be derived from cells of the subcommissural organ. This entity was first described in 2003 [2] and subsequently included in the World Health Organization (WHO) classification of central nervous system tumors [3]. Because data on long-term outcome are lacking, definite histopathological grading of PTPR has not yet been established. Furthermore, the role of adjuvant radiotherapy and chemotherapy in treatment of PTPR remains uncertain. We therefore examined outcome and response to therapy in a series of 44 PTPR patients from France, Germany, Great Britain, Switzerland, Japan, and Slovenia; data for 37 have already been published [4–13], but have been updated.

Materials and methods

Patients

The study was based on a series of 44 patients (21 males and 23 females) diagnosed with PTPR and treated between January 1979 and November 2008. These cases were treated at 28 neurosurgical centers in Europe and two in Japan. Some of the cases have been previously reported [4–13]. The histopathology was reviewed according to current WHO criteria [3]. Cases had often been previously misinterpreted as choroid plexus tumors (7 cases), pineal parenchymal tumors (8 cases), ependymomas (13 cases), or miscellaneous other tumor entities (6 cases); only 10 were initially diagnosed as PTPR. Routine immunohistochemical studies included reactivity with antibodies against neurofilament, synaptophysin, chromogranin-A, neuron-specific enolase, epithelial membrane antigen, glial fibrillary acidic protein, S-100 protein, vimentin, and cytokeratins. Additionally, in some cases, studies included staining for microtubule-associated protein 2 as well as choroid plexus tumor markers Kir 7.1 and stanniocalcin-1 [5]. Data on clinical course and treatment were collected by the participating centers and submitted in an anonymous format following good clinical practice and respecting local laws. Data were updated until the last follow-up or death. One patient was lost to follow-up 15 months after diagnosis. Tumor size was assessed using magnetic resonance imaging (MRI) and/or computerized axial tomography (CT) scans in the 32 cases for which imaging data were available for review. The median diameter of tumors prior to treatment was calculated. The presence of hydrocephalus and tumor extension toward the peduncles, third ventricle, thalamus, lateral ventricles, and cerebellum was assessed. In some cases, postoperative imaging was available for assessment of residual disease before further treatment.

Statistics

Quantitative data are presented as the median and range. When no information was available, status was coded as missing data. Censored data were described using Kaplan–Meier estimation and consisted of the number of patients, number of events, percentage survival, and the 95 % confidence interval (CI). Survival intervals were censored at the date of the last known patient contact. Progression-free survival (PFS) and overall survival (OS) were measured from the date of the first treatment for PTPR (surgical resection or radiotherapy or chemotherapy) to, respectively, the date of first recurrence or death (not considered as a relapse). Statistical comparisons of censored data were performed using the Log-Rank test or Cox proportional hazard model. Smoothing splines were used to predict death risk versus age. Statistical analyses were two sided and performed using R-2.5.0 for Windows.

Assessment of tumor response

Tumor response was based on serial measurements of post-contrast enhanced zones on the post operative CT scan or MRI. When possible, chemotherapy was also correlated with response. Criteria for response to radiotherapy or chemotherapy were defined as follows: a complete response (cr) as the disappearance of the tumor, a partial response (pr) as a 50 % or greater decrease in tumor size, progression of disease (pd) as a greater than 25 % increase in tumor size or any appearance of new tumor sites, and stable disease (sd) as all other situations. The reported site of relapse was the first site of disease progression observed during follow-up.

Results

Patient characteristics

The characteristics of individual patients and the group as a whole are summarized in Tables 1 and 2, respectively. The age of the patients at first treatment ranged from 5 to 66 years (median 29 years), the group comprised 36 adults and 8 children (under 18 years). On average, more than 9 months had passed from the appearance of the first symptoms until the establishment of diagnosis. The most common symptom at presentation was an increase in intracranial pressure with hydrocephalus ($n = 31$); other frequent symptoms were Parinaud's syndrome, ataxia, and

Table 1 Characteristics, treatments, and status of the individual patients

Case	Age (years)	Sex	Size (mm)	Follow up (months)	Surgery	Initial treatment	Dose (pineal) (grays)	Recurrences				Status
								1st	2nd	3rd	4th	
1	19	M	27	106	B, GTR			L	L			Alive
2[a]	28	F	23	138	B, PR	RT	54	L	Brain			Alive pr
3	56	F	35	23	GTR	RT	60	L				Dead
4	53	M	32	91	B	SRS	12	L	L			Dead
5	34	F	40	16	PR			Sp				Dead
6	42	F	26	36	B, GTR	RT, CT	54	L	L			Dead
7[a]	43	M	27	18	PR	RT	na	L				Dead (suicide)
8[a]	14	M	na	0	GTR							LTF
9	32	M	30	198	GTR			L				Alive
10[a]	66	M	na	104	GTR	RT	na	L				Dead
11[a]	62	M	25	25	PR	RT	56					Dead
12	38	F	na	15	GTR			L				Alive
13	23	F	40	111	B, PR			L	L			Alive
14	24	F	na	61	B, GTR	CT, RT	na	L				Alive
15	29	F	25	7	B	RT	50					Dead
16	27	M	50	4	B	RT	55					Dead
17	33	F	20	77	B, PR	CT, RT	60	L				Alive
18	22	F	22	58	B, PR			L				Alive
19	46	F	na	99	B, GTR	RT	60					Alive
20	45	F	18	47	2 B, PR			L	Brain			Alive
21	24	M	na	44	GTR							Alive
22	5	F	28	61	GTR	CT		L,	LV + Sp	Sp		Dead
23[b]	13	M	na	33	B, GTR	RT	50					Alive
24[a]	14	M	50	122	GTR	CT		L	L	L	L	Alive
25[a]	35	M	28	58	PR	RT	56					Alive
26[a]	29	M	48	21	B	RT	42	Brain, Sp				Dead
27[a]	11	F	32	115	B, GTR	RT	54	L	L			Alive pd
28[a]	28	F	5	43	B, GTR							Alive cr
29[a]	26	F	30	166	B	Brachy	60	L + 4^{th}V	L	L		Alive
30[a]	29	F	17	82	GTR	RT	57.5					Alive
31[a]	25	M	40	178	GTR			L	L + 4^{th}V,	L + 4^{th}V		Alive
32	7	F	na	95	GTR	RT, CT	54					Alive cr
33[c]	15	M	30	3	B, GTR							Alive cr
34	16	F	na	21	PR	CT, RT	na					Alive sd
35[d]	21	M	25	198	B, GTR	RT	50	Cereb	Cereb	L		Alive pd
36[e]	33	M	45	67	PR	RT	55	L				Alive pr
37[f]	29	F	36	41	B, GTR	Presurg RT	50					Alive cr
38	36	F	na	45	PR, GTR	RT	na	L				Alive pd
39[g]	42	F	na	14	B							Alive
40	44	M	20	17	GTR	RT	54					Alive cr
41	48	M	27	2	B, GTR	RT	50					Alive cr
42	52	F	na	36	B, PR	SRS	na	L				Alive
43	56	M	20	53	GTR							Alive cr

Table 1 continued

Case	Age (years)	Sex	Size (mm)	Follow up (months)	Surgery	Initial treatment	Dose (pineal) (grays)	Recurrences				Status
								1st	2nd	3rd	4th	
44[h]	43	M	25	28	GTR	CT, RT	60					Alive cr

Cases 1–31 have been reported by Fevre Montange et al. [4] using the same case numbers

Cases 1–23, 25, 35, 39, 42 were treated in France; cases 24–32, 34, 38, 43 in Germany; case 33 in Slovenia; cases 36, 41 in Great Britain; cases 37, 44 in Japan; and case 40 in Switzerland

B biopsy, *Brachy* brachytherapy, *Cereb* cerebellar, *cr* complete response, *GTR* gross total resection, *CT* chemotherapy, *L* local recurrence, *LTF* lost to follow up, *LV* lateral ventricle, *na*, not available, *pd* progressive disease, *pr* partial response, *PR* partial resection, *Presurg*, presurgical, *RT* radiotherapy, *sd* stable disease, *Sp* spinal recurrence, *SRS* stereotactic radiosurgery, *4thV* fourth ventricle

[a] cases also reported by Hasselblatt et al. [5]

[b] case also reported by Buffenoir et al. [6]

[c] case reported by Jeruc and Popovic [7]

[d] case reported by Lechapt-Zalcman et al. [8]

[e] case reported by Santarius et al. [9]

[f] case reported by Amemiya et al. [10] and Shibahara et al. [11]

[g] case reported by Fevre Montange et al. [12]

[h] case reported by Inoue et al. [13]

Table 2 Grouped characteristics of the patients and treatments

	Median (range)	Number of patients	Percent
All patients		44	100
Sex			
Male		21	47.7
Female		23	52.3
Tumor size (mm)	27.5 (5–50)		
Age at first treatment (years)	29 (5–66)		
Type of surgery			
Biopsy		6	13.6
Gross total resection		26	59.1
Partial resection		12	27.3
Chemotherapy			
Yes		8	18.2
No		36	81.8
Radiotherapy			
Yes		28	63.6
No		16	36.4
Radiotherapy dose (Grays)	54 (12–60)		

isolated diplopia. On MRI, most cases showed a lesion of the pineal region (case 22 is illustrated in Fig. 1) with strong contrast enhancement (Fig. 1a). The median tumor diameter was 27.5 mm (5–50 mm, $n = 32$). Extension toward the peduncles, the third ventricle (Fig. 1b, d), thalamus, lateral ventricles, or cerebellum was noted in three cases initially and in four cases at recurrence. Three cases (case 5 initially, cases 22 and 26 at recurrence) showed evidence of spinal cord seeding of tumor cells (case 22 is illustrated in Fig. 1d, e).

Surgery

Whether surgery was performed was determined by the clinical history of the patient and the local preferences and policies of the participating centers. Of the 44 patients, 28

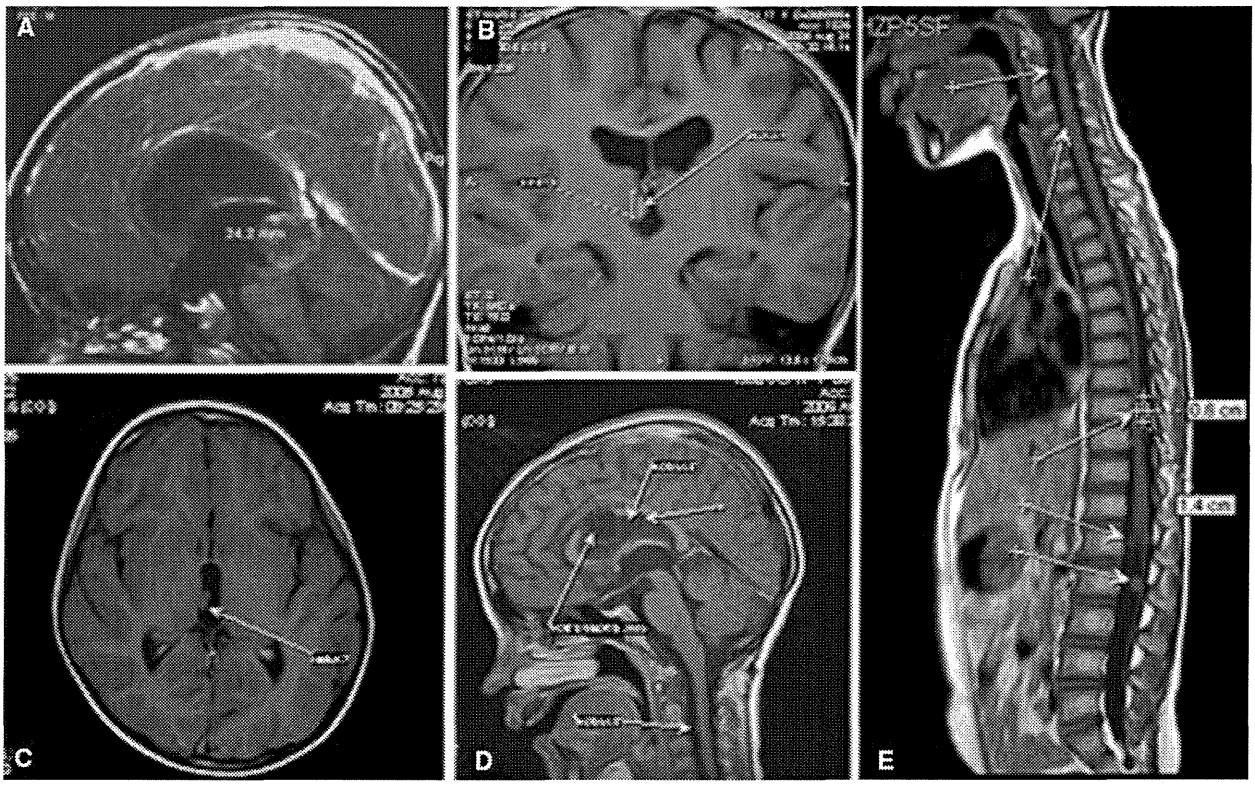

Fig. 1 Magnetic resonance imaging features in case 22. All images are T1-weighted gadolinium-enhanced magnetic resonance imaging scans. **a** Sagittal image of the lesion at presentation, showing a 28 mm (largest diameter) mass in the pineal region prior to first surgery (total tumor removal). Coronal (**b**) and axial (**c**) images showing a first recurrence in the right part of the third ventricle 2 years after the first surgery. Four years after the second surgery, the patient developed multiple nodules in both lateral ventricles (**d**) and in the spine (**e**) visible on sagittal images

underwent either cerebrospinal fluid shunt procedures ($n = 22$) or ventriculocisternostomy ($n = 6$). Tumor resection was more often performed via an infratentorial-supracerebellar approach than via a transcallosal approach. Gross total resection was achieved in 26 patients (11 after biopsy and 1 after partial resection) and partial resection was achieved in 12 (6 after biopsy). In 6 patients, only a biopsy was performed. Because of local recurrence, 14 patients had a second surgical intervention, 10 of which resulted in gross total resection and 4 in partial resection. Eight patients underwent a third operation because of tumor recurrence (gross total resection in 5 and partial resection in 3).

Radiotherapy

The method of radiotherapy delivery was based on the protocol of each center and on the initial diagnosis. Treatments consisted of craniospinal irradiation with a boost to the primary site, whole brain radiotherapy with a boost to the primary site, focal irradiation of the pineal area only, and radiosurgery. Twenty-eight patients received radiotherapy: 3 craniospinal irradiation with a boost applied to the primary site, 1 whole brain radiotherapy with a boost applied to the primary site, 22 focal irradiation of the pineal area (one received brachytherapy with 125-iodine), and 2 radiosurgery. The median pineal dose (which was known in 22 of the 26 irradiated cases) was 54 Gy (CI 95 %: 12.0–60.0 Gy). Despite relatively high cumulative doses (more than 100 Gy in 3 cases), irradiation-related side effects were rare. In one case, thalamic radionecrosis was associated with diplopia and hypersomnia, while, in another, radiosurgery of the recurrence (without prior irradiation) caused thalamo-tectal radionecrosis, leading to motor deficiency and Parinaud's syndrome.

Chemotherapy

Adjuvant chemotherapy (mainly based on cisplatinum-VP16 protocols) was applied in 4 adults and 4 children. Following resection, 4 patients without residual tumor received adjuvant chemotherapy with carboplatin-VP16-vincristine ($n = 3$) or temozolomide ($n = 1$). Two patients (cases 17 and 34) who underwent incomplete tumor