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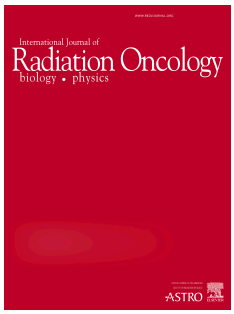

Exclusive Hyper-fractionated Radiotherapy and reduced boost volume for standard-risk medulloblastoma: pooled analysis of the two French multicentric studies MSFOP98 and MSFOP 2007 and correlation with molecular subgroups

Christian Carrie, Virginie Kieffer, Dominique Figarella-Branger, Julien Masliah-Planchon, Stéphanie Bolle, Valérie Bernier, Anne Laprie, Stéphane Supiot, Julie Leseur, Jean-Louis Habrand, Claire Alapetite, Christine Kerr, Christelle Dufour, Line Claude, Sophie Chapet, Aymeri Huchet, Pierre-Yves Bondiau, Alexandre Escande, Gilles Truc, Tan Dat Nguyen, Caroline Pasteuris, Céline Vigneron, Xavier Muracciole, Franck Bourdeaut, Romain Appay, Bernard Dubray, Carole Colin, Céline Ferlay, Sophie Dussart, Sylvie Chabaud, Laetitia Padovani, on behalf of the French Group of Pediatric Radiotherapy (GFRP) and the French Society of Pediatric Cancers (SFCE)

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Excl

medulloblastoma: pooled analysis of the two French multicentric studies MSFOP98 and MSFOP 2007 and correlation with molecular subgroups

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Conflict of interest:

The authors declared no potential conflicts of interest.

Author contributions:

All authors declare to have participated to the recruitment, results and discussion, have seen and approved the final version.

Ms Sylvie Chabaud was responsible for statistical analysis.

Data sharing statements

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Purpose

Medulloblastoma has recently been characterized as a heterogeneous disease with four distinct molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3 and group 4, with new definition of risk stratification. We report progression-free survival, overall survival, and long-term cognitive effects in children with standard–risk medulloblastoma exclusively treated with hyper-fractionated radiotherapy (HFRT), reduced boost volume, online quality control, and we explore the prognostic value of biological characteristics in this chemotherapy-naive population.

Patients and Methods

Patients with standard–risk medulloblastoma enrolled in two successive prospective multicentric studies MSFOP 98 and MSFOP 2007 received exclusive HFRT (36Gy, 1Gy/fraction BID) to the cranio-spinal axis followed by a boost at 68Gy restricted to the tumor bed (1.5 cm margin), with online quality assurance prior to treatment. Patients with MYC or MYCN amplification were not excluded at the time of the study. We report PFS and OS in the global population, and according to molecular subgroups as per WHO 2016 molecular classification, and present cognitive evaluations based on Wechsler scale.

Results

Data from 114 patients included in the MSFOP 98 trial from Dec 1998 to Oct 2001 (N= 48), and in the MSFOP 2007 from Oct 2008 to July 2013 (N= 66) were analyzed. With a median follow-up of 16.2 (range 6.4–19.6) years for the MSFOP 98 cohort and of 6.5 (1.6–9.6) years for the MSFOP2007 cohort, 5-year overall survival (OS) and progression-free survival (PFS) in the global population were 84% (74-89) and 74% (65-81) respectively. Molecular classification was determined for 91 (WNT [N=19], SHH [N=12], and Non-WNT/non-SHH [N=60] –including Group 3 [N=9], Group 4 [N=29], not specified [N=22]). Our results showed more favorable outcome for WNT-activated subgroup and a worse prognosis for SHH-activated patients. Three patients had isolated extra-CNS relapse. The slope of neurocognitive decline in the global population was shallower than that observed in patients with normo-fractionated regimen combined with chemotherapy.

Conclusion

HFRT led to 5 year-survival rate similar to other treatments combined with chemotherapy, with a reduced treatment duration of only six weeks. We confirm MSFOP 98 results, and the prognostic value of molecular status in patients with medulloblastoma, even in the absence of chemotherapy. IQ is more preserved in children with medulloblastoma who received exclusive HFRT and reduced local boost, IQ decline is delayed compared with patients receiving standard regimen. HFRT may be appropriate for patients who do not consent or are not eligible to prospective clinical trials or for patients from developing countries for whom aplasia or ileus may be difficult to manage, in a context of high cost/effectiveness constraints and for whom shortened duration of RT may be easier to implement.

Keywords Medulloblastoma, hyperfractionated radiotherapy, craniospinal irradiation, cytogenetic prognostication, prognosis, risk-assessment, pediatric radiotherapy, quality assurance.

Introduction

Medulloblastoma is the most common malignant childhood brain tumors, accounting for 15 to 20% of all childhood primary central nervous system (CNS) tumors. Nearly half of medulloblastoma occur below 5 years of age. Risk groups have been defined based on a combination of clinical, histopathological, and cytogenetic features. High-risk medulloblastoma were defined by lepto-meningeal metastasis and/or partial resection with a residue >1.5cm^2, and/or large cell or anaplastic histology and/or more recently MYC/MYCN amplification; the absence of all these unfavorable factors defined the standard-risk group.[1,2[

Standard treatment entails surgery followed by craniospinal irradiation with a boost to the whole posterior fossa to prevent dissemination along the craniospinal axis (CSA).[3[Combined treatment with chemotherapy for metastatic medulloblastoma has been proposed to improve outcome, or with the aim of decreasing late sequelae and preserve neuro-cognitive outcome in standard-risk medulloblastoma, through reduced dose of craniospinal irradiation.[4[The standard dose of irradiation on CSA was defined as 36Gy at 1.8Gy once daily followed by a boost up to 54Gy in the posterior fossa,[5[and allow to cure about 60% of standard-risk medulloblastomas. However, a high frequency of severe adverse events including neuro-cognitive effects, decreased bone growth, and hormonal dysfunctions have been reported. The management of standard-risk medulloblastoma has evolved in the last 15 years and currently combines chemotherapy with reduced dose craniospinal irradiation (23.4Gy on CSA followed by a boost of 54Gy restricted to the tumor bed).[6[The event-free survival at 5 years now reaches 65% to 77%.[7[However, craniospinal irradiation at very low dose (18Gy) ~~as~~ investigated in children aged from 3 to 7 years in the COG ACNS03331 trial increased relapse rate, –and demonstrated that very low dose of craniospinal irradiation was not appropriate for all patients.[8[

The use of modern technology for staging, image-guided dosimetry with magnetic resonance imaging (MRI) and computed tomography-scan (CT) registration, and quality assurance in radiotherapy contributed to improve results.[9[The role of chemotherapy in the management of standard-risk medulloblastoma became controversial following the publication of MSFOP 98

online radiotherapy quality control and no chemotherapy in 48 evaluable patients. Indeed, with a median follow up of 77 months, 6-year Overall survival (OS) and Progression-Free Survival (PFS) were 78% (95%CI 66-90) and 75% (95%CI 62-87) respectively, with less pronounced full scale intelligence quotient (FSIQ) decrease~~drops being less pronounced~~. Nevertheless, the limited sample size remains a critical issue. The *French group of pediatric oncology* was involved in the randomized trial SIOP-PNET4 comparing hyperfractionated and conventional radiotherapy in patients with standard-risk medulloblastomas from 2001 to 2008,[7[and in the PNET5 clinical trial which started to enroll patients only in 2013 (NCT02066220). In the meantime, based on MSFOP98 promising results, the *French group of pediatric oncology* decided to treat standard-risk patients according to the MSFOP98 protocol and collected data in an observational study MSFOP 2007 with respect to MSFOP98 inclusion criteria, quality control for radiotherapy, and neuro-cognitive evaluations.

In early 2010, molecular subgroups of medulloblastomas have been defined with different prognostic values after standard treatment all including chemotherapy.[11-13[Nowadays, the World Health Organization (WHO) 2016 classification of the CNS describes distinct medulloblastoma entities based on specific histological and molecular features. The histopathological examination assigned tumors to one of the four entities: classic, desmoplastic/nodular (DNMB), tumors with extensive nodularity (MBEN), or large cell/anaplastic histology (LC/A), based on morphological criteria. The molecular classification identifies four distinct entities: WNT-activated, SHH-activated including *TP53* wildtype and mutant sub-entities, Group 3 (driven by MYC over-expression occasionally related to *MYC* amplification) and Group 4. The current molecular subgroups gather cells from distinct origin and histology. While WNT-activated subgroup characterization includes cells from lower rhombic lip, SHH-activated subgroup more often comprises granule cell precursors, group 3 subgroup gathers often primitive progenitor cells, and group 4 mainly unipolar brush cells.[14[Patients with SHH-activated tumors are more likely to locally relapse than patients in group 3 or group 4 for whom relapses rarely occur locally but rather through metastatic dissemination. SHH-activated tumors with *TP53* mutation are

low-risk tumors [15[; other molecular subgroups *per se* are not yet considered for treatment stratification in ongoing trials investigating combined chemotherapy and irradiation. Histologic subtype and molecular profiling of patients with medulloblastoma helps to promote the development of tailored treatment and to potentially improve overall survival. However, the side effects of current therapies are still a major obstacle, and increased vigilance to better preserved neurocognitive outcomes should also be considered.

We decided to use the revised WHO 2016 tumor classification of the CNS to reclassify patients from the two series MSFOP 98 and MSFOP 2007 and explore prognostic factors in patients exclusively treated with radiotherapy. We additionally explored correlation with neuro-cognitive outcome.

Met

Studies and Patients

Patients with standard-risk medulloblastoma, defined as patients without meningeal enhancement of the brain or the spine, no tumor cells within the craniospinal fluid as per evaluation not sooner than 14 days after resection, and with a maximum residual disease of <1.5cm² in the posterior fossa after surgery, were included in the MSFOP 98 trial between December 1998 and October 2001 (N=48), and in the observational study MSFOP 2007 from October 2008 to July 2013 (N=66). The MSFOP 98 results have been previously published.[10[To note, *MYC/MYCN* amplification and large cell/anaplastic histology had not been considered as exclusion criteria, since their prognostic value was not yet identified at that time. Mandatory investigations included pre-operative MRI, early postoperative CT or MRI of the brain (*i.e.* within 72 hours after surgery), and negative post-operative fluid cerebrospinal examination.

No chemotherapy was administrated before or after surgery and radiotherapy. All CT and MRI scan were retrospectively reviewed by an expert advisory committee of radiologists from xxx

MSFOP 98 and MSFOP 2007 studies were performed in 19 authorized institutions accredited by the xx for paediatric radiotherapy, according to the declaration of Helsinki and the International conference on Harmonization on Good Medical Practices after local approval (Ethics committee of xxx). All patients and/or parents provided written informed consent before enrolment.

Procedures

Patients received hyperfractionated radiotherapy (HFRT)(36Gy- 36 fractions BID, with a minimal interval of 6 hours) on craniospinal axis, followed by a boost with conformal therapy restricted to the tumor bed plus 1.5 cm of safety margin (68Gy- 68 fractions BID); none received additional chemotherapy. A central review of all patients was carried out within 72 hours before treatment initiation, by two experts to physicians providing local treatment. The RT records of the craniospinal irradiation (CSI) were sent by rapid courier until 2012, and used a web-based platform from 2013 (Aquilab software, Loos, France).

Neuropsychological evaluations

the SFCE Neuropsychology Group in 2003[16[, the original publication reported assessments at 4 timepoints (1, 3, 5, and 7 years) to collect enough assessments in each comprehensive cancer center. Real-life assessments were performed at different timepoints to address specific educative requirements. Neurocognitive assessments were performed in children at the end of each three educative cycles to assess graduation or help in referring to specific education class.

Intelligence quotient (IQ) were estimated according to the age-appropriate Wechsler scales,[17,18[using Full scale intelligence quotient (FSIQ) as a reliable measure of overall cognitive functioning, verbal comprehension index (VCI) for verbal reasoning and conceptual abilities, working memory index (WMI) to measure attention abilities, and processing speed index (PSI) to evaluate the speed of graphomotor and mental processing.[16,18[To note, perceptual reasoning/organization index was not used because comparisons using Wechsler scales were not possible.

Histological and molecular classification

One sample of formalin-fixed paraffin embedded (FFPE) specimens from initial biopsy or surgical resection was sent for central review ~~[13[~~to assess histological and molecular/genetic characterization.[13[The histologic characterization of medulloblastomas includes four groups: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity, and large cell/anaplastic medulloblastomas. Molecular classification used several immunohistochemical and molecular markers according to Ellison and collaborators.[19[

WNT-activated medulloblastoma were identified by the presence of beta-catenin nuclear expression (1/200 dilution of polyclonal antibody, Dako, M353901) and 1/100 dilution of filamin expression (clone PM6/317, Fitzgerald/Interchim 10R-F113A), and confirmed by at least one of the following techniques, Sanger direct DNA sequencing assessing *CTNNB1* mutation (n=10), and/or NanoString signature (n=9) (NanoString nCounter Analysis system, NanoString Technologies, Seattle, WA) and/or monosomy 6 determined using the Thermofisher OncoScan® CNV Assay (n=13) (Thermo Fisher Scientific, Waltham, MA, USA). *MYC* and *MYCN* amplification were investigated in 54 cases using the OncoScan assay. No *MYC* amplification was identified, and *MYCN* amplification

was

this exclusion criteria was not known at that time. SHH-activated medulloblastoma were diagnosed through identification of combined expression of 1/3000 dilution of GAB1 (clone EPR375, Ref 133486) and filamin (Abcam, Paris, France). SHH-activated status was confirmed using NanoString signature (n=8) and/or *PTCH1* deletion determined using the OncoScan assay (n=8). *TP53* mutation was searched in only three cases with sufficient and high quality material. Non-WNT/non-SHH medulloblastomas relies on lack of beta-catenin nuclear expression associated with lack of filamin, and GAB1 immunostaining. In addition to immunochemistry, NanoString technics were used to further subtype into Non-WNT/non-SHH medulloblastoma group 3 or group 4, when sufficient material was available. NanoString subgroups were searched using previously published signature.[12[RNA extraction from formalin-fixed paraffin-embedded (FFPE) tissue were performed using RNA isolation kit (Roche, Meylan, France). Subgroup assignment was done by calculation of the proportion of counts specific for each group. A subgroup was attributed if the highest proportion exceeded 70%.

Statistical analysis

Individual data from the two studies MSFOP 98 and MSFOP 2007 were pooled together.

Overall survival was calculated from the date of the first day of irradiation to the date of the death or censored at the date of last follow up for patients alive.

Progression Free Survival is defined as the time from initiation of irradiation until the date of first event; events are defined as the first progression or death (by any cause in the absence of progression). Second malignancies have been exclusively collected through the reasons for death and were not considered in the endpoint. For patients who were not progressive or dead at the time of analysis, follow-up was censored at the time of last contact.

PFS and OS were estimated using the Kaplan-Meier method, and described in terms of median if reached, or using 5-year and 10-year timepoints, along with the associated 2-sided 95% confidence interval (Cis) for the estimates. PFS and OS distributions were compared according to molecular classification using a Log-Rank test, stratified on study parameter.

Neu

assessment was used to compare the four cognitive functioning parameter (FSIQ, VCI, WMI and PSI) according to molecular subgroup, gender and cerebellar mutism syndrome. Degree of significance between subgroups was assessed by Wilcoxon or Kruskal Wallis non parametric tests. Multivariate analysis of Full scale intelligence quotient (FSIQ) according to molecular subgroups and gender was performed to take into account of the difference in gender ratio between molecular subgroups, using analysis of variance including these 2 factors as well as the interaction between these 2 factors.

Res

Patients and tumor characteristics

The global analysis considered 114 patients, including 48 patients enrolled in the MSFOP 98, and 66 patients in the MSFOP 2007 study. The median age was 9.9 years (range: 5-17.5) and the male to female ratio was 1.7 in the global population.

Histopathological and molecular classification was performed in 91 patients. None of the centrally reviewed cases identified anaplastic/large cell histology.

Classification led to 19 WNT-activated classic medulloblastoma, 12 SHH-activated (classic [n=2], desmoplastic/nodular [n=9], and medulloblastoma with extensive nodularity [n=1]. *TP53* was tested *a posteriori* in 3 out of 12 SHH-activated tumors and identified two *TP53-wt* and one *TP53*-mutant which nevertheless remained in the study. Finally, the 60 tumor samples identified as Non-WNT/non-SHH were reclassified in group 3 (n=9, all classic medulloblastoma), group 4 (n=29, all classic medulloblastoma), Non-WNT/non-SHH not otherwise specified (n=22). (Table 1).

The median age in the WNT-activated group was 10.5 years (range 5.3-14.3), 8.25 years (5.2-13.6) in the SHH-activated group, 9.5 years (5-12.7) in group 3, 9.3 years (5.4-13.8) in group 4, and 9.8 (5.2-17.5) in Non-WNT/non-SHH not otherwise classified. To note, the sex ratio was reversed in the WNT-activated group with more females.

Patients with identified molecular profiles had mainly central tumors (n=78), 6 patients had lateralized tumors, and 7 patients had diffuse tumors. Our series showed that WNT-activated and non-WNT/non-SHH group 3 were mainly central tumors, SHH-activated subgroup showed more lateralized tumors, and Non-WNT/non-SHH group 4 included more diffuse tumors.

Treatment

Radiotherapy treatments were performed in the 19 authorized French pediatric cancer centers. The median delay between surgery and radiotherapy was 42 (20-123) days, the mean duration of treatment was 45 days, the median dose to the boost was 68Gy and 36Gy for the spinal axis delivered with 1Gy/fraction BID.

Tole

Radiation Therapy Oncology Group classification of the acute toxicities, grade 2 and grade 3 toxicities were observed during radiotherapy including 10 (8.8%) thrombopenia, 31 (27.2%) neutropenia, 6 (8.3%), anemia, and 22 (19.3%) skin toxicity. One patient with grade 2-3 mucositis, and three with dysphagia were detected. No grade 4 toxicity was reported. No patients received HFRT under general anesthesia.

O*utcomes*

With a median follow-up of 16.2 years (range 6.4 to 19.6) in the MSFOP 98 study and of 6.5 years (1.6 to 9.6) in the MSFOP 2007 study, the PFS and OS at 5 years are respectively 84% (95%CI: 74-89) and 74% (95%CI 65-81) among the 114 evaluable patients (Figure 1A and 1B).

~~29~~ 33 patients died from disease progression (n=29) and ~~four of~~ from secondary cancer (n=4) (three glioblastoma (Non-WNT/non-SHH (N=1); WNT-activated without status on *CTNNB1* mutation (N=1); SHH-activated with no determined *TP53* status (N=1)), and one mesenchymal chondrosarcoma of cauda equina in WNT-activated subgroup.

Relapse patterns

We observed 33 recurrences, including 3 exclusive extra-CNS bone/bone marrow, 3 extra-CNS (bone/bone marrow) associated with diffuse CNS, 2 isolated tumor bed recurrences, 1 in the posterior fossa outside of the tumor bed, and 24 spinal axis and/or diffuse within the CNS with no local recurrence. (Table 2)

Of note, PFS included a total of 37 events.

The median time to recurrence was 25.8 (4.8-158.9) months in the global population. Patients with extra-CNS relapse had a time to relapse of 26, 26, and 45 months respectively. Four relapsing patients are long-term survivors, still in complete remission at 21, 21, 22, and 68 months respectively after salvage treatment (Non-WNT/non-SHH [N=2], WNT [N=1], and without biomolecular analysis [N=1]).

Outcome analysis according to molecular subgroups

activated, 60 Non-WNT/non-SHH-activated (Group 3 [N=9]; Group 4: [N=29], not specified [N=22]).

The 5y-OS according to molecular subgroups was 95% (95%CI 68-99) for WNT-activated group, 67% (95%CI 34-86) for the SHH-activated group, 81% (95%CI 68-89) for Non-WNT/non-SHH subgroup as a whole, 78% (95%CI 36-94) for the group 3, 78% (95%CI 57-90) for the group 4, and 86% (95%CI 63-95) for Non-WNT/non-SHH not otherwise specified.(Figure2)

The PFS was respectively 84% (95%CI 59-95), 67% (34-86), and 71% (58-81) at 5 years for WNT-activated, SHH-activated, and Non-WNT/non-SHH (group 3, group 4, and not classified) (p=0.55) respectively (Figure 2). The PFS was respectively 84% (95%CI 59-95), 56% (23-79), and 67% (53-78) at 10 years. No difference was found in the Non-WNT/non-SHH subgroup (Group 3, 4 and not specified)(Figure S1).

No significant difference was observed in the pattern of relapse according to molecular subgroup: one isolated tumor bed relapse was observed in the SHH- activated subgroup, and one in the Non-WNT/non-SHH group 4. Isolated extra-CNS relapses were identified in Non-WNT/non-SHH group (N=2) and one in the group without specified biomolecular characterization (N=1). The three extra- and intra-CNS were seen in Non-WNT/non-SHH group 3 (N=1) and Non-WNT/non-SHH group 4 (N=1), and Non-WNT/non-SHH not specified (N=1).(Table 2)

Cognitive evaluation

Neuropsychological assessments were performed in 50 out of 91 patients with molecular classification. We report neurocognitive functions over time according to molecular subgroups, cerebellar mutism, gender, and age in Figure 3. Neurocognitive evaluation was achieved at least once at the predefined timepoints in 31 patients. Full scale intellectual quotient (FSIQ) tend to be more preserved overtime than working memory index (WMI) regardless the molecular subgroups. Regarding the comprehensive verbal index (CVI), abilities were initially within normal range in the different subgroups, and declined with time in the WNT-subgroup. Patients with WNT-activated, and patients with non-WNT/non-SHH tumors had a lower processing speed index (PSI) from

diag

remained in normal range.

The analysis of last post-radiotherapy neuropsychological assessment was available in 42 out of 91 patients, and included 16 girls (Table 3). We identified only PSI as significantly lower index in WNT-activated subgroup (p=0.043). We observed a similar trend for FSIQ decline. No differences between subgroups were observed for CVI and WMI. No statistical difference in patients with cerebellar mutism was observed due to the low number of patients with mutism. Nevertheless, a trend for a worse PSI (67 *versus* 86) and worse WMI (70 *versus* 84) was observed. Our results showed a gender effect with better FSIQ results in males (Male: 91; Female: 87). Females had a statistically lower VCI (95 *versus* 107) (p=0.015) but a less slow PSI (90 versus 77). Patients with cerebellar mutism had 3 WNT-activated, 1 SHH-activated, and two Non-WNT/non SHH Group 4 tumors, and tumors were mainly centrally located.

We explore the impact of gender between molecular subgroups. Multivariate analysis showed a trend (p=0.076) for a lower FSIQ in girls, and especially in the WNT-activated subgroup, even if interaction term was not identified as significant.

FSIQ score <90 was observed in 64% of patients, including 16% of patients with a FSIQ score <70.

Dis

The outcome of standard-risk patients with medulloblastoma has dramatically improved during the last 20 years because of significant advances including better staging, improved radiotherapy ballistic approaches, delivery and enhanced quality assurance, advances in surgery, and in post-operative intensive care. Chemotherapy benefits to patients with high-risk group medulloblastomas. Despite no demonstrated ~~clear~~ benefit in term of survival in standard-risk patients, chemotherapy is nevertheless administrated to allow reduced radiation~~.~~**:** the SIOP 2 trial showed that 5y-OS was 67% in the arm with standard dose (36Gy) *versus* 55% in the arm with low dose (24Gy), regardless of the administration of chemotherapy in both arms [20[. The subset analysis showed that the 5y-EFS was 60% in the RT alone subgroup *versus* 69% in patients with reduced dose, with or without chemotherapy. Despite the study POG/COG investigating standard- and reduced-dose irradiation prematurely stopped for low accrual, more relapse occurred in the reduced dose group than in the standard dose group [5[; However, low dose with chemotherapy *versus* standard dose alone have never been investigated in a randomized study. Nevertheless, based on a 5y-EFS of 81 % evidenced in a monocentric prospective study [21[, reduced dose combined with chemotherapy became the standard, emphasized by neuro-cognitive evaluation showing better intellectual outcome [22[. Recent multicentric studies showed 5y- and 10y-EFS in the range of 70-80 % and 50-60% respectively, coupled with an improvement over time that may be attributed to better selection of patients with localized disease, improved surgical, post-surgical, and radiotherapy management.

With an overall survival and a progression-free survival at five years of respectively 84% [74-90] and 74% [64-81], our series compares favorably with other studies published in this field showing 5y-EFS of 81% (+/-2%) and 5y-OS of 86% (+/-9%),[23[3y-relapse free survival of 83.5% (95%CI 66.1-100%) and 3y-OS of 83.2% (95%CI 65.4-100%) with a median follow-up of 33 (16-58) months, [24[5y-EFS of 77% (+/-4%) and 5y-OS of 85% (+/-3%) with a median follow-up of 4.8 years,[7] and 5y-PFS of 82.2 (+/-2.9) and 5y-OS 85% (+/-2%) with a median follow-up of 6.6 months.[8] In addition, our results are confirmed at 10 years and showed similar 10y-PFS and -OS around 70%. To the best

of k

these results are better than those previously ~~those~~ observed in the MSFOP 93 study with reduced CSA dose ~~and~~ combined with chemotherapy,[25[or in the COG study with 18Gy irradiation [8,23[Moreover, these encouraging results have been achieved whereas patients now considered in high-risk group had been included. Despite the absence of chemotherapy, the rate of extra-CNS relapses was low and comparable with that observed with radiotherapy combined to chemotherapy,[5,6[and we reported a time to relapse in patients with extra-CNS recurrences ~~was~~ similar to that observed in the global population of relapsing patients.

We point out the favorable outcome in four long-term survivors in complete remission after relapse (respectively with 21-, 21-, 22-, 68-month follow-up after progression) suggesting that salvage treatment can be feasible and effective following HFRT.

The hematologic toxicity in patients treated according to MSFOP 98 and MSFOP 2007 studies was very mild with less than 10% of grade 3 adverse events compared with 100% reported in the COG trial.[8[The PNET 4 study reported that 20% of the patients prematurely discontinued chemotherapy for hematological toxicity.[10[With a total duration of 7 weeks, HFRT received in MSFOP 98 and MSFOP 2007 trials was the shortest treatment and potentially cost-effective. In addition, less hematologic toxicities were reported, and may prevent from vincristine related toxicity as reported in PNET4 study.[7] The rate of deaths from secondary malignancies was low with only 4 cases all occurring in irradiated area (glioblastomas [n=3], and sarcoma of cauda equine [n=1]). This approach should be considered as an attractive option especially for patients who do not consent or who are not eligible for prospective clinical trials with chemotherapy, or for patients ~~in~~ from developing countries ~~-~~for whom aplasia or ileus may be difficult to manage, in a context of high cost effectiveness constraints and for whom shortened duration of RT may be easier to implement.

At the time of inclusion in MSFOP studies, only high-risk *versus* standard-risk stratification criteria were used. This risk-based stratification exclusively used clinical parameters and did not take into account the molecular heterogeneity of medulloblastomas. The recent molecular classification

patients with WNT-activated, SHH-activated *TP53-wt*, group 3, group 4, SHH-activated associated with *TP53* mutation, and the worst prognosis for patients with medulloblastoma with large cells or classified in group 3 with *MYC* amplification, taking into account that these patients also received chemotherapy. The scarcity and heterogeneity of the samples in our study has precluded classification based on the only results from immunohistochemistry. In the Non-WNT/non-SHH group, we opted to complement immunohistochemical results with NanoString instead of methylation-based subgrouping for cost-effectiveness. Although we acknowledge that a few samples may have been classified differently using methylation approaches, we are confident that this would only concern a very few Non-WNT/non-SHH cases,[26[and would not jeopardize the main findings of our study. The outcome of WNT tumors, for instance, deserve a particular attention. Patients with WNT-activated tumor enrolled in the John Hopkins trial were not treated with radiotherapy, but exclusively received chemotherapy (NCT02212574) and the risk-adapted craniospinal irradiation is currently being considered in clinical trials, SJMB (NCT01878617), COG (NCT02724579), and SIOP PNET5 (NCT02066220), which systematically combine chemotherapy with decreased doses of radiotherapy. The cognitive evaluation carried out in 42 patients from MSFOP studies confirmed prior results. Indeed, their neurocognitive function and more specifically FSIQ seems to be better preserved at a higher level even if indirect comparison between studies is tricky. Obviously, the potential benefit in neuropsychological outcome can not be exclusively attributed to the HFRT; the absence of chemotherapy preventing any deleterious effect on cognition can also contribute to this favorable outcome.[27[Moreover, it should be mentioned that the SFOP 98 and 2007 protocols restricted the boost to tumor bed, and substantially reduced the exposure level to high-dose of radiation to the supratentorial compartment. As a matter of fact, this region received significantly less radiation dose ~~of~~ >60Gy in a larger volume (212cc *versus* 40cc) compared with former whole posterior fossa boosts,[10[mainly benefiting to temporal and hippocampal area. In previous studies such as MSFOP93, or in the standard arm of the PNET 4 study, no volume reduction had been applied. Moxon and colleagues showed that a limited

irrad

sequelae in medulloblastoma.[28[Further comparisons of efficacy between studies using whole posterior fossa or tumor boost irradiation, remain difficult to address.(Table 4)[24,29,30[We recognized that reporting results from single arm studies do not allow to formally compare neurocognitive outcomes HFRT to other treatments, and obviously randomized trial would be required to confirm these results. Nevertheless, randomized trial are particularly difficult to set up in this specific field. Further studies should also carry out an appropriate collection of all second malignancies.

The benefit of HFRT was marginally confirmed in the randomized PNET 4 trial showing a benefit in verbal IQ in a subgroup of patients <8 years of age receiving HFRT compared with those receiving standard treatment.[29[Moreover, a decline in intellectual functioning over 5 years has already been reported in children treated with standard brain irradiation plus adjuvant chemotherapy.[31[The most frequent neuropsychological deficits include slow processing speed, working memory and attention impairments,[32[and the Full scale intellectual quotient (FSIQ) decline over time with accentuated results observed with higher doses of radiation therapy.[18,33-35[

In our study, neurocognitive outcome (verbal reasoning, conceptual abilities, working memory, and processing speed) vary according to treatment (HFRT), molecular subgroupings, cerebellar mutism, and gender.

HFRT allowed to reduce neurocognitive sequelae over time, and may reduce long-term side-effects on cognitive outcome compared to historical high (35Gy) and standard (25Gy) radiation doses.[18[Median FSIQ of 88 (40-131) remained within the low average normal value, our series showed a FSIQ ~~score~~ <90 ~~was observed~~ in 64% of the patients including 16% of the patients with a FSIQ <70, whereas FSIQ <90 has been reported in only 25% ~~in~~ of the global population, including 2.2% with FSIQ <70.[17,18[Our results are consistent with those previously reported by Gupta and collaborators.[24[HFRT without upfront chemotherapy preserved cognitive functioning with only 15% of children with mild mental retardation (FSIQ <70). Our study showed a 4-point decrease at 5 years, consistent with the favorable neurocognitive outcome, with a slightly larger FSIQ decrease at

5 y

treatment.[30[

In addition, we report for the first time, as far as we know, results on working memory that were not previously assessed. Working memory regardless of the molecular subgrouping or cerebellar mutism is an area of particular concern. Its deterioration over the first 5 years previously described by Knight and collaborators,[36[actually seems to being extended far beyond 10 years after diagnosis regardless of the molecular subgroup.

Moxon and collaborators,[31[reported a distinct functional outcome in patients with SHH-activated, and patients with Non-WNT/non-SHH tumors.[28[WNT-activated tumors appears to have the worst outcome but our series showed that 33% of the patients with WNT-activated tumor suffered from cerebellar mutism, and were mainly girls (79%). These results should be interpreted with caution given the reduced sample size in each group. Determination of molecular subgroup has not been achieved in all patients due to sample unavailability or technical constraints. Cognitive evaluations at all predefined timepoints had not been always possible, and data were mainly collected to address education schedule requirement. Our sample size was too small to argue the difference in cognitive sequelae by molecular subtypes. But it is still suggestive because we report long term follow-up data.

Cerebellar mutism after cerebellar tumor surgical resection has already been reported as a risk factor for worse long-term outcomes. Our study did not evidence statistical difference in patients with cerebellar mutism which may be due to the reduced number of patients. Nevertheless, cerebellar mutism seems to decrease neurocognitive function and we observed 19-point difference in processing speed index between patients with or without cerebellar mutism. The risk of mutism has been reported to associated with the central localization of the tumor.[37[Our series showed that patients who experienced cerebellar mutism had different molecular profiles, and did not allow to evidence any correlation between mutism and molecular subgroup. We nevertheless more frequently observed a deteriorated neurocognitive outcome in patients with cerebellar mutism in the WNT-activated subgroup, who more often present with centrally located tumors.[28,35,38-42[

Multivariate analysis shows lower FSIQ in girls compared to boys even after adjustment on molecular subgroups, and could also explain the worst cognitive outcome of WNT-activated subgroup, in which girls are overrepresented.

According to the linear quadratic model 68Gy given through 1Gy BID is equivalent to 62Gy for α/β ratio of 10, and 54.4 for α/β ratio of 3. The 36Gy given on the same schedule on CSA is biologically equivalent to 33Gy for tumor effect and 28.8 Gy with α/β ratio of 3 for late effect: further studies using the same hypotheses should investigate radiation exposure of 24Gy in 24 fractions of 1Gy BID in CNS, allowing to achieve an equivalent biological dose of 22Gy for tumor efficacy, close to the normo-fractionated schedule (23.4Gy) but presumably only ~~18~~19.2Gy for long-term side effect with an assumed α/β ratio of 3 for the late toxicity effect, and of 10 for tumor effect.[43~~37~~[Such approach deserves closer analysis specifically in the WNT subgroup.

Conclusion

HFRT and reduced tumor boost led to survival rate similar in standard-risk group medulloblastoma than in more aggressive medulloblastoma treated with normo-fractionation followed by one-year chemotherapy, according to the new prognostic classification (i.e. WHO 2016). Our results also evidence an improved hematological tolerance, and an alleviated treatment length, beneficial both to patients and medical staff. Furthermore, our results suggest that the neurocognitive function is substantially spared by HFRT associated with restricted boost, and no chemotherapy.

Our results confirm the prognostic value of the WHO 2016 biomolecular classification in a chemotherapy- naive population, treated with an exclusive escalated dose administered with altered fractionation. Further investigations with reduced doses of HFRT alone, or combined with low dose of chemotherapy are warranted.

Legends

Table 1. Patient characteristics.

Table 2. Pattern of relapses in the global population.

Table 3. Neuropsychological results according to molecular subgroups, cerebellar mutism, and gender, based on last post-radiotherapy assessment.

Table 4. Irradiation dose, irradiation localization, Full scale intellectual quotient (FSIQ), and overall survival rates in patients with medulloblastoma.

Figure 1. Progression free survival and overall survival. Kaplan-Meier plot for (A, C) Progression free survival and (B, D) overall survival, in the global population and in the two studies MSFOP 98 and MSFOP 2007, respectively. Data cutoff was June, 15, 2019. PFS included a total of 37 events (33 relapses and 4 deaths from second cancer)

Figure 2. A) Progression free survival and B) overall survival, according to molecular subgroups,

Figure 3. Full scale intellectual quotient (FSIQ), verbal comprehension index (VCI), working memory index (WMI), and processing speed index (PSI) changes over time for patients in the global population, and according to A) molecular subgroups, B) mutism, C) gender, and D) age. Molecular subgroup: WNT-activated (n=10), SHH-activated (n=7), Non-WNT/non-SHH(n=33); Cerebellar mutism: without mutism (n=44), with mutism (n=6); Gender: male (n=30), female (n=20); Age: <9 years (n=25), ≥9 years (n=25).

Supplementary data online only.

Figure S1. Progression free survival (A), and overall survival (B) in Non-WNT/non-SHH subgroups group 3, group 4, and not otherwise specified.

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Table 1. Patient characteristics in the global population of patients enrolled in MSFOP 98 and MSFOP 2007 (N=114), including the 91 patients for whom histopathological and molecular classification has been achieved.

Characteristics	Global population MSFOP 98 and MSFOP 2007 (N=114)	Patients with histopathological and molecular classification (N=91)
Age, year (range)	9.9 (5-17.5)	9.60 (5.00-17.50)
Gender		
Male	71 (62.3%)	55 (60.4%)
Female	43 (37.7%)	36 (39.6%)
Histological status		
Classic	102 (89.5%)	71
Desmoplastic and nodular	12 (10.6%)	9
Tumor localization		
Centralized	/	78
Lateralized	/	6
Diffuse	/	7
Mutation status		
WNT-activated,	/	19 (20.9%)
SHH-activated,	/	12 (13.2%)
Non-WNT/non-SHH group 3	/	9 (9.9%)
Non-WNT/non-SHH group 4	/	29 (31.9%)
Non-WNT/non-SHH, not specified subgroup	/	22 (24.2%)
Relapses	33 (28.9%)	27 (29.6%)
Isolated extra-CNS	3	2
Extra- and intra-CNS	3	3
Isolated tumor bed failure	2	2
PF outside of tumor bed	1	1
Other*	24	19
Median time to relapse, months (range)	25.8 (4.8-158.9)	17.2 (4.8-158.9)

CNS: Central nervous system; PF: Posterior fossa. *Craniospinal axis, diffuse, central nervous system fluid, supratentorial compartment.

Table 2. Pattern of relapses in the global population, according to molecular subgroups.

	WNT-activated (N=19)	SHH-activated (N=12)	Non-WNT/ non-SHH Group 3 (N=9)	Non-WNT/ non-SHH Group 4 (N=29)	Non-WNT/ non-SHH not specified (N=22)	Without molecular analysis (N=23)
Isolated extra-CNS	0	0	0	0	2	1
Extra- and intra-CNS	0	0	1	1	1	0
Isolated tumor bed failure	0	1	0	1	0	0
PF outside of tumor bed	0	0	0	0	1	0
Other*	3	3	2	8	3	5

CNS: central nervous system; PF: Posterior Fossa; *Craniospinal axis, central nervous system fluid, supratentorial compartment.

Table 3. Neuropsychological results according to molecular subgroups, cerebellar mutism, gender, and age, based on last post-radiotherapy assessment.

	Full scale Intelligence quotient **(FSIQ)**	Verbal comprehension index **(VCI)**	Working memory index **(WMI)**	Processing speed index **(PSI)**
All				
N	39	42	30	42
Median (Min-Max)	88 (40-131)	96 (45-134)	81 (50-114)	84.50 (50-111)
Molecular subgroups				
WNT-activated				
N	6	8	5	8
Median (Min-Max)	80.5 (40-126)	94 (45-127)	82 (50-106)	74 (50-106)
SHH-activated				
N	7	7	7	7
Median (Min-Max)	94 (85-101)	96 (86-108)	80 (70-106)	96 (88-100)
Non-WNT/non-SHH				
N	26	27	18	27
Median (Min-Max)	88.5 (57-131)	101 (65-134)	82.50 (61-114)	78 (50-111)
Kruskal-Wallis test	*P = 0.343*	*P = 0.346*	*P = 0.793*	*P = 0.043*
Cerebellar mutism				
Without cerebellar mutism				
N	34	36	26	36
Median (Min-Max)	88 (66-131)	97 (65-134)	83.5 (68-114)	86 (50-111)
With cerebellar mutism				
N	5	6	4	6
Median (Min-Max)	90 (40-126)	84 (45-127)	70 (50-112)	67 (50-106)
Wilcoxon nonparametric test	*P = 0.966*	*P = 0.397*	*P = 0.299*	*P = 0.249*
Gender				
Male				
N	26	26	18	26
Median (Min-Max)	91 (66-131)	107 (65-134)	81 (68-114)	77 (50-106)
Female				
N	13	16	12	16
Median (Min-Max)	87 (40-100)	95 (45-108)	82.5 (50-106)	89.5 (50-111)
Wilcoxon nonparametric test	*P = 0.184*	*P = 0.015*	*P = 0.340*	*P = 0.288*
Age				
<9 years				
N	18	20	13	20
Median (Min-Max)	87.5 (40-126)	96 (45-127)	79 (50-106)	80 (50-96)
≥9 years				
N	21	22	17	22
Median (Min-Max)	88 (57-131)	99 (69-134)	86 (61-114)	86 (50-111)
Wilcoxon nonparametric test	*P = 0.844*	*P = 0.300*	*P = 0.357*	*P = 0.307*

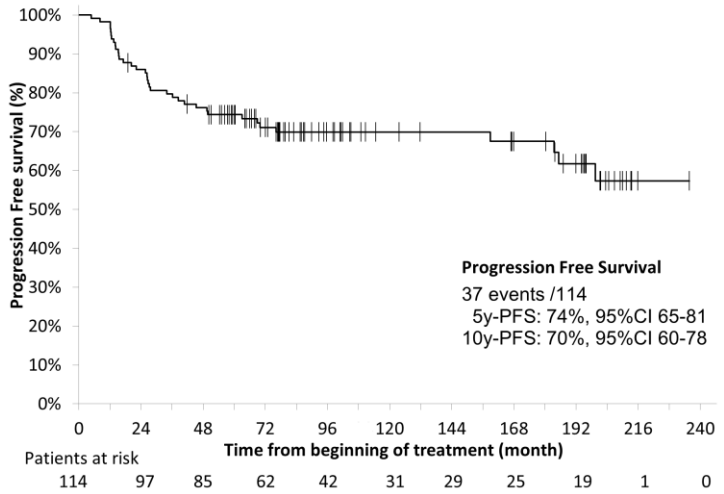
Table 4. Irradiation dose, irradiation localization, Full scale intellectual quotient (FSIQ), and overall survival rates at 5 year (5y-OS) in patients with medulloblastoma.

	Number of patients evaluable (subgroup of interest/global cohort)	Irradiation dose	Irradiation localization (Tumor bed or posterior fossa)	FSIQ	5y-OS
MSFOP 98/2007 [Carrie *et al.* 2020[	39/114	Exclusive radiotherapy (68Gy BID) No chemotherapy	Tumor bed	88 (40-131)	84%
PNET4 normo-STRT [29[	66/340	54Gy normo-STRT + Chemotherapy	Posterior fossa	86 (40-122)	85% (NS)
PNET4 HFRT [29[	71/340	68Gy BID + Chemotherapy	Posterior fossa + boost 8Gy	90 (65-128)	87% (NS except in patients <8y)
Proton radiotherapy [30[	54/59	54Gy GyRBE + Chemotherapy	Posterior fossa + boost	-1.5/year At 5 year: 97	83%
TATA memorial [24[	20	68Gy BID No chemotherapy	Tumor bed	90 (72-99)	83%

STRT: Standard radiation therapy; HFRT: Hyperfractionated radiation therapy; GyRBE: Gray radiobiological equivalents; NS: non significant.

Figure 1.

A



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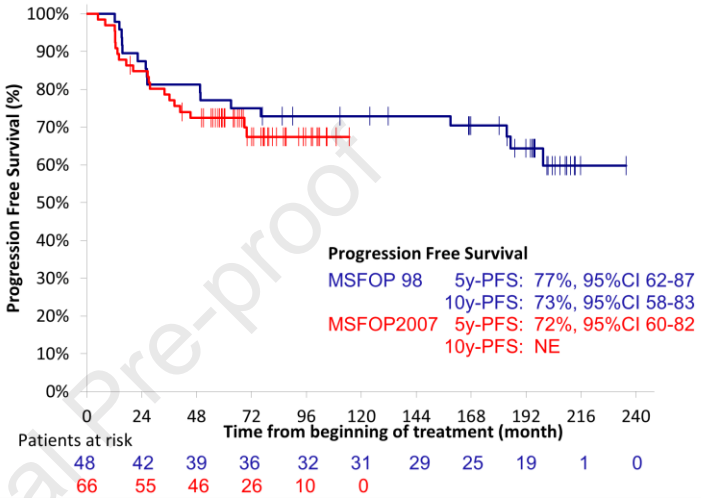

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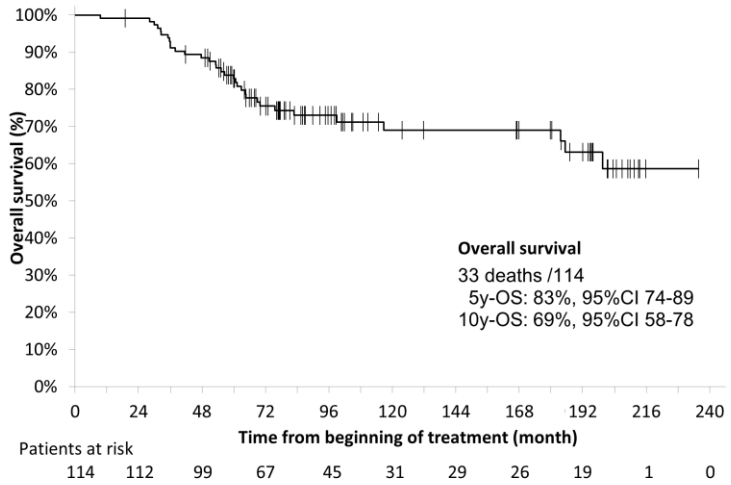


D

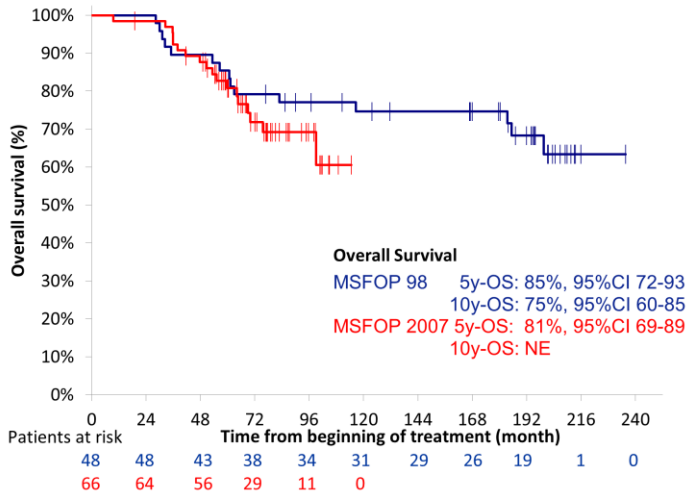
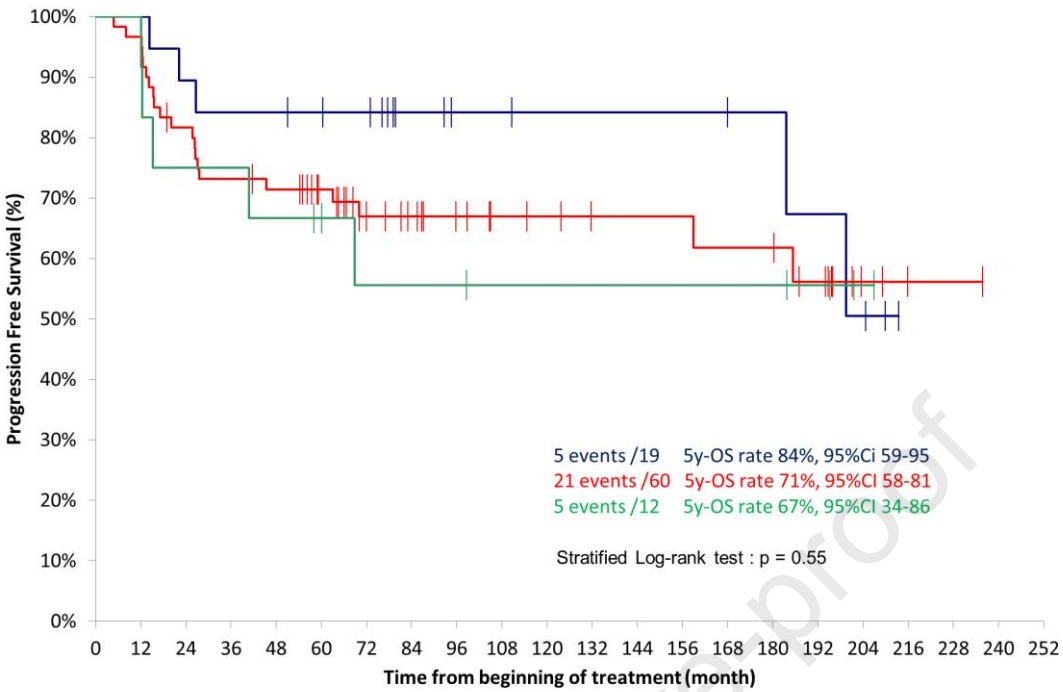


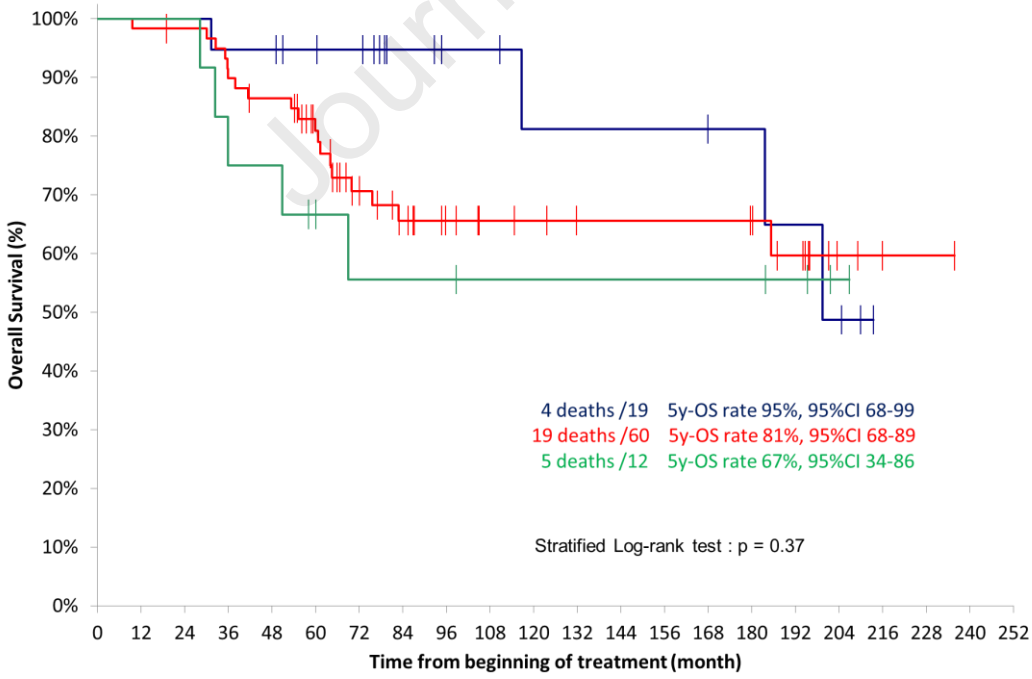
Figure 2.

A



Patients at risk										
WNT-activated	19	17	16	14	7	6	6	5	4	0
Non-WNT/non SHH	60	48	41	27	19	15	13	12	9	1
SHH-activated	12	9	8	5	5	4	4	4	3	0

B



Patients at risk										
WNT-activated	19	19	18	15	8	6	6	5	4	0
Non-WNT/non SHH	60	58	50	30	19	15	13	13	9	1
SHH-activated	12	12	9	5	5	4	4	4	3	0