

Mise au point sur les essais thérapeutiques SFOP/SFCE versus SIOP (délai entre protocoles : français devenus SIOP)

Médulloblastomes

HGG

LGG

Epéndymomes

TGM

MB SR > 5 ans MSFOP 98

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Online Quality Control, Hyperfractionated Radiotherapy Alone and Reduced Boost Volume for Standard Risk Medulloblastoma: Long-Term Results of MSFOP 98

Christian Carrie, Jacques Grill, Dominique Figarella-Branger, Valerie Bernier, Laetitia Padovani, Jean Louis Habrand, Mohamed Benhassel, Martine Mege, Marc Mahé, Philippe Quetin, Jean Philippe Maire, Marie Helene Baron, Pierre Clavere, Sophie Chapet, Philippe Maingon, Claire Alapetite, Line Claude, Anne Laprie, and Sophie Dussart

PATIENTS AND METHODS

Between December 1998 and October 2001, 55 patients with standard-risk medulloblastoma (defined as patients without meningeal enhancement of the brain or the spine, no tumor cells within the craniospinal fluid, and with a maximum residual disease of $< 1.5 \text{ cm}^2$ in the posterior fossa after surgery) were enrolled in the MSFOP 98 protocol. Mandatory investigations included:

55 pts 2¹¹ a

Rôle du bifrac, qui sera testé dans le PNET 4

Résultats actualisés avec MSFOP 2007

	MSFOP98 N=48	MSFOP2007 N=66	ALL N=114
ISOLATED EXTRA CNS	1	2	3
INTRA AND EXTRA CNS	2	1	3
ISOLATED TUMOR BED	1	1	2
FCP OUTSIDE TB	0	1	1
OTHER :spi.axis, diffuse, cns fluid , sustent	10	14	24

Protocols	OS5 (%)	PFS5 (%)
HFRT MSFOP 98 + 2007	84	74
HFRT PNET 4	87	77
Normof MSFOP 93	73	65

MB < 5 ans BB SFOP

Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children

Jacques Grill, Christian Sainte-Rose, Anne Jouvét, Jean-Claude Gentet, Odile Lejars, Didier Frappaz, François Doz, Xavier Rialland, Fabienne Pichon, Anne-Isabelle Bertozzi, Pascal Chastagner, Dominique Couanet, Jean-Louis Habrand, Marie-Anne Raquin, Marie-Cécile Le Deley, Chantal Kalifa, on behalf of the French Society of Paediatric Oncology (SFOP)

Summary

Background Morbidity and mortality are high in young children with medulloblastoma who receive craniospinal radiotherapy. We aimed to assess whether adjuvant treatment with protracted chemotherapy alone could replace radiotherapy.

Methods We enrolled 79 children aged younger than 5 years who had had surgical resection of medulloblastoma onto a multicentre trial. Patients were treated with combination chemotherapy, which did not include methotrexate, for more than 16 months irrespective of the extent of disease. Early postoperative imaging defined three groups: R0M0 (no residual disease, no metastasis), R1M0 (radiological residual disease alone), and RXM+ (presence of metastases). Patients who did not relapse did not receive radiotherapy. Patients who relapsed or had disease progression received salvage treatment, which consisted of high-dose chemotherapy and stem-cell transplantation followed by local or craniospinal radiotherapy. For children classified as R0M0, the primary endpoint was 5-year overall survival and the secondary endpoint was 5-year progression-free survival. For children classified as R1M0 or RXM+, the primary endpoint was best radiological response and the secondary endpoints were 5-year overall survival and 5-year progression-free survival. Analyses were done by intention to treat.

Findings Two of 15 patients classified as RXM+ and four of 17 patients classified as R1M0 had a complete radiological response. 5-year progression-free survival was 29% (95% CI 18–44) in the R0M0 group, 6% (1–27) in the R1M0 group, and 13% (4–38) in the RXM+ group. 5-year overall survival was 73% (59–84) in the R0M0 group, 41% (22–64) in the R1M0 group, and 13% (4–38) in the RXM+ group. In the R0M0 group, 5-year progression-free survival was 41% (26–58) for the 34 patients who underwent gross total resection compared with 0% for the 13 patients who had subtotal resection (relative risk 2.7 [1.3–5.6], $p=0.0065$).

Interpretation Conventional chemotherapy alone can be used to cure children with non-metastatic medulloblastoma who have gross total resection confirmed by early radiological assessment, but is not sufficient for treatment of those with metastatic or incompletely resected medulloblastoma. Salvage treatment followed by posterior-fossa radiotherapy can effectively treat local relapses or progression.



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See [Reflection and Reaction](#) page 541

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Department of Paediatric and Adolescent Oncology (J Grill PhD, M-A Raquin MD, C Kalifa MD), Department of Diagnostic Radiology (D Couanet MD), Department of Radiotherapy (Prof J-L Habrand MD), and Department of Biostatistics (M-C Le Deley PhD), Institute Gustave Roussy, Villejuif, France; Department of Neurosurgery, Necker Hospital for Sick Children, Paris, France (Prof C Sainte-Rose MD); Department of Pathology, Wertheimer Hospital, Lyon, France (A Jouvét MD); Department of Paediatric Oncology, University Hospital Centre, Marseille, France (J-C Gentet MD); Department of Paediatric Haematology/Oncology, University Hospital Centre, Tours, France (O Lejars MD); Department of

Results

From January, 1990, to December, 2002, 93 patients were treated according to the BBSFOP (Baby Brain French Society of Paediatric Oncology) protocol with an initial diagnosis of medulloblastoma in 18 centres in France, one centre in Belgium, and one centre in the UK (figure 1). Recruitment was stopped early for patients classified as RXM+ (in 1995) and R1M0 (in 1996) because of insufficient response.

75 pts 13¹¹ a
OS₅ 73% sans RT si R0M0

MB SR > 3 ans SFCE

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Standard-Risk Medulloblastoma Treated by Adjuvant Chemotherapy Followed by Reduced-Dose Craniospinal Radiation Therapy: A French Society of Pediatric Oncology Study

V. Oyharcabal-Bourden, C. Kalifa, J.C. Gentet, D. Frappaz, C. Edan, P. Chastagner, E. Sariban, A. Pagnier, A. Babin, F. Pichon, S. Neuenschwander, M. Vinchon, D. Bours, V. Mosseri, C. Le Gales, M. Ruchoux, C. Carrie, and F. Doz

From the Institut Curie, Paris; Institut Gustave Roussy, Villejuif; Centre Hospitalo-Universitaire (CHU) La Timone, Marseille; Centre Léon Bérard, Lyon; CHU Rennes, CHU Nancy; CHU Grenoble; CHU Strasbourg; Centre Oscar Lambret, Lille; CHU Lille; Unité de la Recherche Médicale U537, Le Kremlin Bicêtre, France; and Hôpital Reine Fabiola, Brussels, Belgium.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to François Doz, MD, Department of Pediatric Oncology, Institut Curie, 26 Rue d'Ulm, 75231 Paris Cedex 05, France. e-mail: Francois.Doz@curie.net

ABSTRACT

Objective

The primary objective of this study was to decrease the late effects of prophylactic radiation without reducing survival in standard-risk childhood medulloblastoma.

Patients and Methods

Inclusion criteria were as follows: children between the ages of 3 and 18 years with total or subtotal tumor resection, no metastasis, and negative postoperative lumbar puncture CSF cytology. Two courses of eight drugs in 1 day followed by two courses of etoposide plus carboplatin (500 and 800 mg/m² per course, respectively) were administered after surgery. Radiation therapy had to begin 90 days after surgery. Delivered doses were 55 Gy to the posterior fossa and 25 Gy to the brain and spinal canal.

Results

Between November 1991 and June 1998, 136 patients (median age, 8 years; median follow-up, 6.5 years) were included. The overall survival rate and 5-year recurrence-free survival rate were 73.8% ± 7.6% and 64.8% ± 8.1%, respectively. Radiologic review showed that 4% of patients were wrongly included. Review of radiotherapy technical files demonstrated a correlation between the presence of a major protocol deviation and treatment failure. The 5-year recurrence-free survival rate of patients included in this study with all optimal quality controls of histology, radiology, and radiotherapy was 71.8% ± 10.5%. In terms of sequelae, 31% of patients required growth hormone replacement therapy and 25% required special schooling.

Conclusion

Reduced-dose craniospinal radiation therapy can be proposed in standard-risk medulloblastoma provided staging and radiation therapy are performed under optimal conditions.

RESULTS

One hundred thirty-six patients (80 boys, 56 girls) were included between November 1991 and June 1998. The median age was 8 years (range, 3 to 18 years). Data were updated in June 2003, with a median follow-up of 6.5 years (range, 2 months to 10.5 years). For the 96 patients last known to be alive, the median time elapsed between last follow-up and June 30, 2003 is 17 months.

136 pts 7⁷ a
Désescalade RT → 25 Gy
EFS₅ 66%, OS₅ 75%

MB PNET 4 SR SIOP

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial

Birgitta Lannering, Stefan Rutkowski, Francois Doz, Barry Pizer, Göran Gustafsson, Aurora Navajas, Maura Massimino, Roel Reddingius, Martin Benesch, Christian Carrie, Roger Taylor, Lorenza Gandola, Thomas Björk-Eriksson, Jordi Giralt, Foppe Oldenburger, Torsten Pietsch, Dominique Figarella-Branger, Keith Robson, Marco Forni, Steven C. Clifford, Monica Warmuth-Metz, Katja von Hoff, Andreas Faldum, Véronique Mosseri, and Rolf Kortmann

RESULTS

Between January 1, 2001, and December 31, 2006, 340 patients were randomly assigned, starting in Germany where the study originated and gradually accruing across Europe. One ependymoma and one atypical teratoid rhabdoid tumor were excluded because of ineligible histology at central review leaving 338 randomly assigned patients.

340 pts 6 a

Pas de différence HFRT vs RT

EFS₅ 77% OS₅ 87%

EFS₅ : R+ 82%

R- 64%

HFRT associated with marginally higher VIQ in < 8 y

MB HR > 3 ans SFOP



Treatment of high risk medulloblastomas in children above the age of 3 years: A SFOP study[☆]

J. Verlooy^a, V. Mosseri^a, S. Bracard^b, A. Lellouch Tubiana^c, C. Kalifa^d, F. Pichon^e, D. Frappaz^f, P. Chastagner^b, A. Pagnier^g, A.-I. Bertozzi^h, J.C. Gentetⁱ, E. Sariban^j, X. Rialland^k, C. Edan^l, D. Bours^a, M. Zerah^c, C. Le Gales^m, C. Alapetite^a, F. Doz^{a,n,*}

3. Results

3.1. Study population

Between January 1993 and June 1999, 115 patients with an institutional diagnosis of high risk medulloblastoma were eligible for inclusion. Age at diagnosis of the 115 included

115 pts 6⁵ a
8 en 1/CBDCA-VP - 36 Gy
EFS5 50%, OS5 60%.
R+ only EFS 69%
M1 59%
M2/M3 43%

MB PNET 3 HR SIOP



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www.ejconline.com

Outcome for patients with metastatic (M2–3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy

Roger E. Taylor ^{a,*}, Clifford C. Bailey ^b, Kathryn J. Robinson ^c,
Claire L. Weston ^c, David A. Walker ^d, David Ellison ^e, James Ironside ^f, Barry L. Pizer ^g,
Linda S. Lashford ^h, on behalf of the United Kingdom Children's Cancer Study Group
(UKCCSG) Brain Tumor Committee

3. Results

3.1. Patient population

Between March 1992 and January 2000, a total of 68 patients with M2–3 MB were registered with the UKCCSG and treated with CT and RT according to the PNET-3 protocol. The largest number of patients, 49 (72%), was entered from UKCCSG centres. Patients were also entered from the following countries: Denmark: 1 (2%), The Netherlands: 8 (12%), Poland: 3 (4), Spain: 7 (10%).

68 pts 7⁹ a
EFS₅ 35% OS 44%
Rôle délai RT

MB < 5 a IGR

Pediatr Blood Cancer 2014;61:907–912

**High-Dose Busulfan–Thiotepa With Autologous Stem Cell Transplantation Followed
by Posterior Fossa Irradiation in Young Children With Classical or Incompletely
Resected Medulloblastoma**

Guillaume Bergthold, MD,^{1,2} Maria El Kababri, MD,³ Pascale Varlet, MD, PhD,⁴ Frederic Dhermain, MD, PhD,⁵
Christian Sainte-Rose, MD, PhD,⁶ Marie-Anne Raquin, MD,¹ Virginie Kieffer, MS,^{1,7} Gisele Goma, MS,⁸
Jacques Grill, MD, PhD,¹ Dominique Valteau-Couanet, MD, PhD,¹ and Christelle Dufour, MD^{1*}

19 pts

Bu-Tpa + RT focale

EFS₃ 68% OS₃ 85%

MB HR / rechutes / réfractaires

High-dose Chemotherapy With Autologous Stem Cell Rescue Followed by Posterior Fossa Irradiation for Local Medulloblastoma Recurrence or Progression After Conventional Chemotherapy

Vita Ridola, MD¹
Jacques Grill, MD, PhD¹
Francois Doz, MD, PhD²
Jean-Claude Gentet, MD³
Didier Frappaz, MD⁴
Marie-Anne Raquin, MD¹
Jean-Louis Habrand, MD, PhD⁵
Christian Sainte-Rose, MD⁶
Dominique Valteau-Couanet, MD, PhD¹
Chantal Kalifa, MD¹

BACKGROUND. The objective of the current study was to determine the outcome of children with local recurrence or progression of medulloblastoma in patients who received high-dose chemotherapy (HDC) and posterior fossa (PF) irradiation.

METHODS. HDC consisted in busulfan at a dose of 600 mg/m² and thiotepa at a dose of 900 mg/m² followed by autologous stem cells transplantation (ASCT). PF radiotherapy was delivered at doses from 50 grays (Gy) to 55 Gy on Day +70 after ASCT. Twenty-seven patients developed local recurrence of an initially completely resected medulloblastoma. Twelve patients had local residual disease after surgery and were enrolled into the salvage protocol at the time of local disease progression under conventional chemotherapy.

39 pts

OSs 69%

local recurrence OSs 77%

Pediatr Blood Cancer 2014;61:1398–1402

Tandem High-Dose Chemotherapy and Autologous Stem Cell Rescue in Children With Newly Diagnosed High-Risk Medulloblastoma or Supratentorial Primitive Neuro-Ectodermic Tumors

Christelle Dufour, MD,^{1*} Virginie Kieffer,^{1,2} Pascale Varlet, MD, PhD,³ Marie Anne Raquin, MD,¹ Frederic Dhermain, MD, PhD,⁴ Stephanie Puget, MD, PhD,⁵ Dominique Valteau-Couanet, MD, PhD,¹ and Jacques Grill, MD, PhD¹

Background. To assess the feasibility and effectiveness of high-dose chemotherapy (HDC) with stem cell support followed by conventional craniospinal radiotherapy (RT) as treatment for children older than 5 years of age with newly diagnosed high-risk medulloblastoma (MB) or supratentorial PNET (sPNET). **Procedure.** Between May 2001 and April 2010, 24 children older than 5 years of age (MB = 21; sPNET = 3), fulfilling inclusion criteria at diagnosis, were treated at Gustave Roussy. After conventional chemotherapy, they received two courses of high-dose thiotepa (600 mg/m²) followed by craniospinal RT. **Results.** The median follow-up was 4.4 years

(range, 0.8–11.3 years). For children with metastatic MB, the 5-year event-free survival (EFS) and overall survival (OS) were 72% and 83%, respectively. The toxicity was manageable. No toxic death occurred. At the most recent evaluation, among the 24 children who had at least one Full Scale Intellectual Quotient (FSIQ) examination at a median follow-up of 3.79 years after diagnosis, the mean estimated FSIQ was 82 (range, 56–114). **Conclusions.** In children with metastatic MB, tandem HDCT with ASCT followed by conventional craniospinal RT proved its feasibility without jeopardizing survival. *Pediatr Blood Cancer* 2014;61:1398–1402. © 2014 Wiley Periodicals, Inc.

24 pts

2 Tpa RT CS

EFSs 72% OSs 83%,

HGG BB SFOP



Review

High-grade glioma in children under 5 years of age: A chemotherapy only approach with the BBSFOP protocol

C. Dufour^{a,*}, J. Grill^a, A. Lellouch-Tubiana^b, S. Puget^c, P. Chastagner^d, D. Frappaz^e,
F. Doz^f, F. Pichon^g, D. Plantaz^h, J.C. Gentetⁱ, M.A. Raquin^a, C. Kalifa^a

3. Results

Patient characteristics are summarised in Table 1.

3.1. Study population

Between October 1990 and June 2002, 21 children (10 boys, 11 girls) were treated for a high-grade glioma with the BBSFOP protocol.

21 pts 11³ a
EFS₅ 32%
27% sans RT

HGG SFOP

Pediatr Blood Cancer 2007;49:803–807

Outcome of Children Treated With Preradiation Chemotherapy for a High-grade Glioma: Results of a French Society of Pediatric Oncology (SFOP) Pilot Study

P. Chastagner, MD, PhD,^{1*} C. Kalifa, MD,² F. Doz, MD, PhD,³ E. Bouffet, MD, PhD,⁵ J.C. Gentet, MD,⁶
M.M. Ruchoux, MD, PhD,⁷ S. Bracard, MD, PhD,⁸ E. Desandes, MD,⁹ and D. Frappaz, MD, PhD⁴

Patient Population

The BCV pilot study was opened to participating SFOP institutions in March 1990 and was closed in May 1996. A total of 73 patients were enrolled from 15 French institutions. Patients' characteristics are presented in Table I.

73 pts, 6³a
RR 20%
EFS₅ 16%

LGG SFOP

RESEARCH ARTICLE

Mortality in Children with Optic Pathway Glioma Treated with Up-Front BB-SFOP Chemotherapy

Josué Rakotonjanahary^{1,2✉}, Emilie De Carli¹, Matthieu Delion³, Chantal Kalifa⁴, Jacques Grill⁴, François Doz⁵, Pierre Leblond⁶, Anne-Isabelle Bertozzi⁷, Xavier Rialland¹, Brain Tumor Committee of SFCE[†]

Patients and Methods

Patients

This is a historical cohort analysis of children less than 16 years of age who were treated in France for an OPG between June 1990 and December 2004. Using the French data base BB-SFOP (which lists all of the children treated in France with BB-SFOP chemotherapy,

Results

Patient characteristics

Between June 1990 and December 2004, a total of 445 children in France were treated with BB-SFOP chemotherapy. There were various indications (this chemotherapy can be applied in young children for brain tumors other than OPGs), and only 182 patients aged less than 16 years were identified as having been treated for OPG, using BB-SFOP chemotherapy as the first-line treatment. Two patients could not be included in the analysis because too much diagnosis data were missing from their records. Finally, our series included 180 children with a median follow-up of 13.6 years (range: 6.1–23.6). The main characteristics of these patients at the time of diagnosis are summarized in [Table 1](#). Among the 180 patients, 79 had a follow-up ≥ 15 years, and 49 had a follow-up ≥ 18 years. Six patients were lost to follow-up (median follow-up: 11.8 years, range: 6.1–14.6).

LGG SIOP

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Available online at www.sciencedirect.com

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Clinical Trial

A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤ 16 years) low grade glioma – A final report

Astrid K. Gnekow ^{a,1}, David A. Walker ^{b,*¹}, Daniela Kandels ^b, Susan Picton ^c, Giorgio Perilongo ^{d,1}, Jacques Grill ^e, Tore Stokland ^f, Per Eric Sandstrom ^g, Monika Warmuth-Metz ^h, Torsten Pietsch ⁱ, Felice Giangaspero ^{j,k}, René Schmidt ^l, Andreas Faldum ^l, Denise Kilmartin ^m, Angela De Paoli ^m, Gian Luca De Salvo ^m, on behalf of the Low Grade Glioma Consortium and the participating centers²

3. Results

3.1. Patient cohort

Between 1st April 2004 and 14th April 2012, 3417 previously untreated patients from 118 institutions in 11 countries were registered at the SIOP-LGG 2004 database following the SIOP-LGG treatment strategy. During the trial period, 1057 patients received chemotherapy. Of these, 497 non-NF1 patients were randomised to receive either VC- (n = 249) or VCE-induction (n = 248) (Fig. 2).

497 pts non NF1
PFS₅ 46% OS₅ 89%
VC = VCE
S. diencephaliques pires

Ependymomes SFOP



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CLINICAL INVESTIGATION

Brain

INTRACRANIAL EPENDYMOMAS IN CHILDREN: SOCIETY OF PEDIATRIC ONCOLOGY EXPERIENCE WITH POSTOPERATIVE HYPERFRACTIONATED LOCAL RADIOTHERAPY

CÉCILE CONTER, M.D.,* CHRISTIAN CARRIE, M.D.,† VALÉRIE BERNIER, M.D.,‡ ANNE GEOFFRAY, M.D.,§
ANNE PAGNIER, M.D.,¶ JEAN-CLAUDE GENTET, M.D.,|| ARIELLE LELLOUCH-TUBIANA, M.D.,#
SYLVIE CHABAUD, M.D.,** AND DIDIER FRAPPAZ, M.D.*

Patient eligibility

Postoperative local HFRT was offered to all children with localized intracranial EP seen between November 1996 and December 2002 in centers affiliated with the French Society of Pediatric Oncology. The criteria for enrollment included age of 5–17 years at diagnosis, EP of any pathologic grade, and written informed consent. The criteria for exclusion were spinal primary EP, disseminated EP, previous chemotherapy or RT, relapse, associated disease, re-

24 pts

60-66 Gy

OS₅ 75%, PFS₅ 54%

Pas de benefice HFRT/RT conv

TGM SFOP

British Journal of Cancer (1999) **79**(7/8), 1199–1204
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Combined treatment modality for intracranial germinomas: results of a multicentre SFOP experience

E Bouffet^{1,*}, MC Baranzelli², C Patte³, M Portas⁴, C Edan⁵, P Chastagner⁶, F Mechinaud-Lacroix⁷, C Kalifa³ on behalf of the Société Française d'Oncologie Pédiatrique

RESULTS (Table 1)

Between January 1990 and December 1996, 99 newly diagnosed patients from 25 centres were enrolled in the SFOP protocol for intracranial GCTs. Fifty-nine were registered in the germinoma study. Other patients were registered in the non-germinomatous intracranial GCT study. Patients with a biopsy-proven germinoma associated with high β HCG secretion and/or α FP secretion were

99 pts

EFS 96 %, OS 98 %

Efficacité CT + RT focale

TGM SIOP

Neuro-Oncology 15(6):788–796, 2013.
doi:10.1093/neuonc/not019
Advance Access publication March 3, 2013

NEURO-ONCOLOGY

SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease

Gabriele Calaminus, Rolf Kortmann, Jennifer Worch, James C. Nicholson, Claire Alapetite, Maria Luisa Garrè, Catherine Patte, Umberto Ricardi, Frank Saran, and Didier Frappaz

Materials and Methods

Patients

A total of 235 patients (176 male, 59 female) with histologically confirmed diagnosis of a germinoma and complete examination were enrolled in SIOP CNS GCT 96 from January 1, 1996 through December 31, 2005,

235 pts

TGM localisées

CSI ou CT + RT focale , PFS5 97 vs 88% = identiques

OS5 95% = identiques

Métastatiques PFS5 98% OS 98%

TGM NG GTC SIOP

Neuro-Oncology

19(12), 1661–1672, 2017 | doi:10.1093/neuonc/nox122 | Advance Access date 5 July 2017

Outcome of patients with intracranial non-germinomatous germ cell tumors—lessons from the SIOP-CNS-GCT-96 trial

Gabriele Calaminus, Didier Frappaz, Rolf Dieter Kortmann, Barbara Krefeld, Frank Saran, Torsten Pietsch, Alexandre Vasiljevic, Maria Luisa Garre, Umberto Ricardi, Jillian R. Mann, Ulrich Göbel, Claire Alapetite, Matthew J. Murray, and James C. Nicholson

Patients

A total of 219 patients were enrolled into the SIOP-CNS-GCT-96 trial, of whom 35 were withdrawn because of incomplete staging and 35 because they did not receive treatment according to protocol (Fig. 1). A total of 149 patients (116 males, 33 females) with malignant NGGCT, confirmed by histology and/or tumor markers and complete workup, were enrolled by December 31, 2005 and followed to December 1, 2014. The median age at diagno-

219 pts

PFS₅ 72% chemotherapy + focal RT

metastatic cases chemotherapy + CS RT

PFS₅ 68%

LCS >1000 ng/mL = risk factor

R+ not resected at the end of treatment

is associated with an increased relapse risk

SFOP/SFCE

- MB SFOP SR > 3 ans
11/1991-06/1998 79 m, 136 pts
1,7 pts/m



0,5 a (10 pts)

- MB SFOP 98 SR > 3 ans
12/1998-10/2001 35 m, 55 pts
1,6 pts/m

MB

SIOP

- MB SIOP PNET 3 SR 3-16 ans
03/1992-01/2000 94 m, 190 pts
2 pts/m



1 a (24 pts)

- MB SIOP PNET 4 SR 3-16 ans
01/2001-01/2007 72 m, 338 pts
4,7 pts/m



8² a (460 pts)

- MB SFOP PNET 5 SR 5-16 ans
03/2015

SFOP/SFCE

MB

SIOP

- MB SFOP HR > 3 ans

01/1993-10-2001 78 m, 115 pts
1,5 pts/m

SFOP/SFCE

HGG

« SIOP »

SFOP HGG > 5 ans

03/1990-06/1996 75 m, 73 pts
1 pts/m

15² a

(182 pts)

HERBY 3-5 ans

10/2011-02/2015 40 m, 121 pts
3 pts/m

BBSFOP HGG < 5 ans

10/1990-06/2002 136 m, 21 pts

18⁵ a

(34 pts)

? SIOP HGG infant

SFOP/SFCE

LGG

SIOP

BB SFOP

06/1990-12/2004 174 m, 445 pts
2,6 pts/m

SIOP LGG 2004

04/2004-04/2012 96 m, 497 pts
5,2 pts/m



7⁷ a

(473 pts SIOP non inclus)

(237 pts SFCE non inclus)

SIOP LGG II

En ?

SFOP/SFCE

Ependymomes

SIOP

Ependymome SFOP Hyperfract > 5 ans SR

11/1996-12/2002 73 m, 24 pts

(> 49 pts non inclus)

SIOP Ependymoma

06/2015

12^6 a



TGM SNC SFOP

08/1990-03/1999 103 m, 99 pts
1 pts/a

TGM

15⁹ a

(189 pts SFOP non inclus)

CNS SIOP « 96 »

01/1996-12/2005 120 m, 235 pts
2 pts/a

12⁹ a (306 pts non inclus)

CNS GTC II

09/2013



[Carboplatin and VP 16 in medulloblastoma: a phase II Study of the French Society of Pediatric Oncology \(SFOP\).](#)

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