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# Metastatic Medulloblastoma: the Experience of the French Cooperative M7 Group

**E. Bouffet, J.C. Gentet, F. Doz, P. Tron, H. Roche, D. Plantaz, A. Thyss, J.-L. Stephan, C. Lasset, C. Carrie, C. Alapetite, M. Choux, C. Mottolese, A. Visot, J.M. Zücker, M. Brunat-Mentigny and J.L. Bernard**

**A retrospective analysis was performed to determine the outcome of children with metastatic medulloblastoma given a standardised treatment programme. Of 68 consecutive patients treated in the French M7 protocol for medulloblastoma, 23 presented with metastatic disease. They were uniformly treated with surgery, and the same protocol of chemotherapy and craniospinal radiotherapy. The 7-year relapse-free survival rate is 43% for metastatic patients compared to 68% for patients with localised disease. Survival did not correlate with age, sex, location of metastases, extent of initial surgery and the dose of radiation therapy on the posterior fossa. Survival did correlate with the dose to the cranial field with a threshold dose of 30 Gy. Patients with metastatic disease have a worse prognosis and require more aggressive therapies at initial presentation. The prognostic impact of the different sites of metastatic disease requires further evaluation in cooperative studies.**

**Key words: medulloblastoma, metastatic disease, chemotherapy, radiotherapy, prognostic factors**
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## INTRODUCTION

DUE TO major advances in surgery, chemotherapy and radiotherapy, the prognosis of medulloblastoma has dramatically improved in the last 20 years. Recent series report an overall disease-free survival at 10 years of 50–60% [1–3]. However, if metastases are present at diagnosis, the survival rate is obviously worse, ranging from 30 to 40% [4]. Moreover, the survival difference between patients with localised and metastatic disease may actually be even greater, since many patients classified as having no metastasis (Mo) had neither cerebrospinal fluid (CSF) cytology examination nor a myelogram at diagnosis. The optimal management for patients with metastatic medulloblastoma at

diagnosis is not well established, as the relevant prognostic factors for these metastatic patients have not been properly analysed. From 1985 to 1988, 68 children with medulloblastoma were evaluated as part of the French Cooperative Medulloblastoma Group, M7. In this paper, we have analysed the group of patients with newly diagnosed metastatic medulloblastoma in whom the disease could be detected by conventional staging procedures, CSF examination, myelogram and/or spinal axis magnetic resonance imaging (MRI), and cranial computed tomography (CT) scan or MRI.

## PATIENTS AND METHODS

68 newly diagnosed, previously untreated patients entered the M7 study between March 1985 and September 1988, in a total of eight centres (Centre Léon Bérard, hôpital Nord, hôpital de la Timone, Centre Claudius Regaud, hôpital Charles Nicolle, hôpital de la Tronche, Institut Curie, Centre Antoine Lacassagne). Among this referral population, 23 of these patients presented with detectable metastatic disease. Metastatic disease was defined according to Chang's criteria, by the presence of malignant cells at CSF examination, and/or macroscopic spinal deposits detected by myelogram or neuraxis MRI, and/or supratentorial localisations. Minimum follow-up in this study was 3.6 years or until death (3.6–8.5 years).

All patients underwent craniotomy with removal of as much diseased tissue as possible. The pathological diagnosis of medulloblastoma was mandatory before initiation of the M7 protocol. Patients were referred as soon as the surgical wound had healed according to the surgeon's decision. Initial staging procedure included clinical examination, review of the operative notes, cranial CT or MRI scan at day 20 postsurgery, and CSF examination at day 21 at the time of myelogram. Patients with metastatic disease were classified as high risk, in the group that included patients with either brain stem involvement or incomplete resection or metastasis.

The M7 protocol for high-risk patients included two courses of the 8-in-1 regimen [5] (methylprednisolone 300 mg/m$^2$, vincristine 1.5 mg/m$^2$, lomustine 75 mg/m$^2$, procarbazine 75 mg/m$^2$, hydroxyurea 1500 mg/m$^2$, cisplatin 60 mg/m$^2$, cytosine arabinoside 300 mg/m$^2$, cyclophosphamide 300 mg/m$^2$) on day 8 and day 21 after surgery. High-dose methotrexate (12 g/m$^2$) with folinic acid rescue was given at day 35 and day 42. Serum methotrexate levels were checked in all patients at 24, 48 and 72 h. Prior to each course of therapy, a complete blood cell count, platelet count, serum creatinine, electrolytes and hepatic enzyme levels were obtained. Schedule modifications for subsequent courses were dependant on the degree of the myelosuppression, and included alteration of timing without modification of drug dosage.

Radiation was initiated during the chemotherapy, overlapping with the two high-dose methotrexate courses. Radiation was administered through two parallel opposed photon beams prescribed at the International Commission of Radiation Unit and Measurement (ICRU) point to the cranial field, at a daily dose of 1.8 Gy with five weekly fractions up to a recommended dose of 27 Gy. A 27-Gy boost was given to the posterior fossa. The superior limit of the infratentorial field was the cerebellar tentorium as defined by the CT scan. Spinal irradiation was delivered with a posterior field at the same fractionation, up to 35 Gy. An additional 10 Gy boost was given locally in the case of spinal or supratentorial metastases. Photon and electron beam were used for the spinal axis. Gap junctions were used between the posterior fossa and spinal axis. One month after the completion of radiation therapy, patients started an additional four courses of 8-in-1 chemotherapy, one course given every 4 weeks. The M7 protocol was approved by each hospital ethical committee.

All patients were followed clinically during and after treatment. A CT scan or MRI of the head, with and without administration of contrast material, was obtained 2 months after the completion of the radiotherapy, and then every 4 months during the first year. The scans were then repeated at 6-monthly intervals. CSF was examined 2 months after the completion of radiotherapy, every 2 months during the first year, and every 4 months during the second year. No specific review was undertaken for spinal metastasis. Complete remission was defined as no detectable abnormality in each of these examinations. Progression was defined as any new lesion detected in any of the examinations. A complete staging (CSF examination, CT scan and myelogram) was performed for relapsing patients.

The imaging records and histopathology of each patient were centrally reviewed as was the quality of radiotherapy for each patient as has been previously reported [5].

We examined the following factors for prognostic significance: age at diagnosis, sex, site of metastasis and extent of disease, dose and delay of radiation therapy and extent of surgery. For all the variables examined, the results are reported in terms of event-free survival. Event-free survival was measured from the time of surgery to the date of relapse/progression or last follow-up. The survival curve was produced using the Kaplan and Meier method [6]. Comparison of groups for a given factor was made using the log-rank test.

## RESULTS

23 patients presented with metastatic medulloblastoma (16 males and seven females). The mean age was 7.5 years (range 18 months to 15 years). According to Chang's classification [7] 6 cases were M1, 2 were M2 and 15 were M3. A practical staging system, based on the results of both CSF examination and myelogram, was formulated. 6 cases had isolated CSF involvement (CSF+); 8 had isolated unique or multiple metastatic spinal deposits (SD), and 9 had an association of CSF+ and SD or supratentorial localisations. Patients' characteristics are shown in Table 1.

All patients underwent resection of the primary tumour. 17 patients had a complete or subtotal resection (based on operative note review and postoperative scans), and 6 had a macroscopic residual mass (partial resection).

Corrspondence to E. Bouffet.
E. Bouffet, C. Lasset, C. Carrie and M. Brunat-Mentigny are at the Department of Paediatric Oncology, Centre Leon Berard, 28 rue Laennec, 69373 Lyon; J.C. Gentet and J.L. Bernard are at the Department of Paediatric Oncology, Hôpital de la Timone, Marseille; F. Doz, C. Alapetite and J.M. Zücker are at the Department of Paediatric Oncology, Institut Curie, Paris; P. Tron is at the Department of Paediatric Oncology, Hôpital Charles Nicolle, Rouen; H. Roche is at the Department of Paediatric Oncology, Centre Claudius Regaud, Toulouse; D. Plantaz is at the Department of Paediatric Oncology, Hôpital de la Tronche, Grenoble; A. Thyss is at the Department of Paediatric Oncology, Centre Antoine Lacassagne, Nice; J.-L. Stephan is at the Department of Paediatric Oncology, Hôpital Nord, Saint Etienne; M. Choux is at the Department of Paediatric Neurosurgery, Hôpital de la Timone, Marseille; C. Mottolese is at the Department of Paediatric Neurosurgery, Hôpital Wertheimer, Lyon; and A. Visot is at the Department of Paediatric Neurosurgery, Hôpital Trousseau, Paris, France.
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*Table 1. Characteristics and outcome of the 23 metastatic patients*

| Case no. | Age (years) | Sex | Stage | Extent of resection | CSF | Myelography RMN | Delay surgery radiotherapy (days) | Radiation dose (Gy) PF | Brain | Site of relapse | Relapse-free period (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14 | M | M1 | Total | + | − | 65 | 55 | 30 | 0 | 2968+ (NED) |
| 2 | 14.5 | M | M1 | Total | + | − | 54 | 55 | 35 | 0 | 2897+ (NED) |
| 3 | 4.5 | F | M1 | Total | + | − | 40 | 54 | 30 | 0 | 2075+ (NED) |
| 4 | 14 | M | M1 | Total | + | − | 43 | 54 | 30 | 0 | 1318+ LFU |
| 5 | 12 | M | M1 | Total | + | − | 29 | 54 | 30 | Brain | 1075 |
| 6 | 8.5 | M | M1 | Total | + | − | 54 | 54 | 27 | CSF, SC | 389 |
| 7 | 7 | M | M3 | Partial | ? | × | 56 | 54 | 27 | 0 | 3075+ (NED) |
| 8 | 8.5 | M | M3 | Partial | − | + | 45 | 54 | 25 | 0 | 2185+ (NED) |
| 9 | 4.5 | M | M3 | Total | − | + | 53 | 54 | 27 | 0 | 2105+ (NED) |
| 10 | 5.5 | M | M3 | Total | − | × | 10 | 54 | 27 | 0 | 1810+ (NED) |
| 11 | 10 | F | M3 | Total | − | + | 50 | 54 | 27 | CSF | 675 |
| 12 | 6 | M | M3 | Total | − | × | 50 | 54 | 27 | Brain | 316 |
| 13 | 5 | M | M3 | Partial | − | + | 58 | 52 | 27 | Brain | 342 |
| 14 | 11.5 | M | M3 | Total | − | × | 60 | 54 | 27 | Brain SC Local | 222 |
| 15 | 3.5 | M | M3 | Total | + | × | 37 | 52 | 30 | 0 | 2133 + (NED) |
| 16 | 12 | M | M2(ST) | Partial | + | − | 49 | 54 | 34 | 0 | 1874 + (NED) |
| 17 | 10.5 | M | M3 | Total | + | + | 50 | 52 | 27 | Brain Local | 1235 |
| 18 | 1.5 | F | M3 | Partial | + | × | 92 | 32 | 16 | Brain | 444 |
| 19 | 7 | M | M3 | Total | + | + | 79 | 54 | 27 | Local | 289 |
| 20 | 6 | M | M3 | Total | + | + | 37 | 54 | 27 | Brain, CSF | 268 |
| 21 | 4.5 | F | M3 | Total | + | + | 54 | 54 | 27 | Local | 252 |
| 22 | 1.5 | F | M2(ST) | Partial | + | × | 45 | 33 | 33 | Local | 152 |
| 23 | 3.5 | F | M3 | Total | + | × | | | | 0 | 91 (toxic death) |

M, male; F, female; NED, no evidence of disease; CSF, positive cerebrospinal fluid cytology; PF, posterior fossa; ST, supratentorial metastasis; LFU, lost to follow-up; SC. +, single deposit; ×, multiple deposits.

Initial chemotherapy was started with a median delay of 13 days (range 6–56) after the surgical procedure. All but 2 patients completed the entire chemotherapy programme: 1 died of a candida fungaemia after the first course of chemotherapy. The second was initially mis-staged and did not receive the postradiotherapy chemotherapy programme.

The median delay from surgery to initiation of radiotherapy was 48 days (range 10–92). One patient had early signs of spinal cord compression and required emergency radiation therapy on day 10. 20 patients received between 52 and 55 Gy to the posterior fossa. 2 patients, less than 2 years of age, had an elective dose reduction. Doses to the spinal axis were administered according to the initial staging for all but these two infants previously mentioned. The doses to the supratentorial area were variable, however, with 14 patients receiving < 30 Gray and 8 ⩾ 30 Gray (Table 1).

Recurrent disease developed in 12/22 evaluable patients (54%). Of 20 sites, the most common site of relapse was supratentorial (7/12 patients, 58%), either isolated (3 cases) or as an associated site (4 cases). The posterior fossa was the only involved site in 3 patients, and was involved in 42% (5/12). The others sites were spinal (3), CSF (3) and multiple sites (5). Median time to relapse was 316 days (range 152–1235). Median follow-up for survivors is 2105 days (range 1810–3075). One patient was lost to follow-up in complete remission after 44 months. All but one who relapsed have died, with a median time from recurrence to death of 108 days (range 0–552).

10 patients (43%) in this series are currently in continuous complete remission, with a median follow-up of 70 months.

Univariate analysis of survival is shown in Table 2. Dose to the cranial field (below versus > 30 Gy) was the only factor with prognostic significance. Females fared worse than males. Female patients had a 7-year event-free survival of 14% compared to a 56% for males ($P = 0.056$). The difference in survival according to the age at diagnosis was not statistically significant. After complete resection of the primary, the probability of survival at 7 years was 41%, compared to 50% after less complete surgery. The size of these two subgroups is too small, however (respectively, 17 and 6 cases), to allow any firm conclusions. There was no radiation dose effect for a total dose to the primary ranging from 33 to 55 Gy, but 20 of the 23 patients received 52–54 Gy. A dose to the whole brain above 30 Gy was, however, associated with a better outcome (Figure 1), and 6 of 7 supratentorial relapses occurred in patients treated with a dose below 30 Gy. The delay to initiate radiation therapy had no clear impact on survival.

*Table 2. Metastatic medulloblastomas: event-free survival* (EFS) *by group*

| Group | No. of patients | Actuarial 7-year EFS | P | |
|---|---|---|---|---|
| Male | 16 | 56% | 0.056 | |
| Female | 7 | 14% | | |
| Age | | | | |
| < 7½ years | 13 | 38% | 0.67 | |
| ⩾ 7½ years | 10 | 48% | | |
| Extent of resection | | | | |
| Total-subtotal | 17 | 41% | 0.78 | |
| Partial | 6 | 50% | | |
| Delay surgery to radiotherapy | | | | |
| ⩾ 48 days | 14 | 36% | 0.54 | |
| < 48 days | 9 | 56% | | |
| Dose to the brain | | | | |
| < 30 Gy | 15 | 27% | 0.05 | |
| ⩾ 30 Gy | 8 | 75% | | |
| Site of metastasis | | | | |
| CSF alone | 6 | 67% | | |
| | | | 0.58 | 0.076 |
| Isolated spinal deposits | 8 | 50% | | |
| | | | 0.20 | |
| CSF + deposits | 9 | 22% | | |

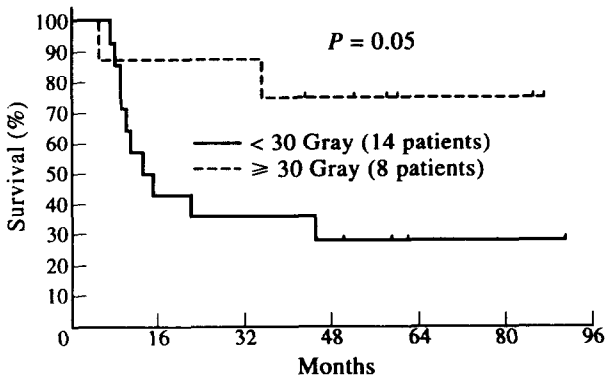


**Figure 1. Event-free survival as a function of radiation dose to the brain.**

The event-free survival according to our staging classification was better for patients with isolated CSF positivity, and worst for patients with both CSF positivity and spinal or supratentorial deposits (Figure 2). No significant difference was observed, although some trends approach statistical significance.

## DISCUSSION

Prognostic factors in medulloblastoma were originally defined many years ago, using the TNM classification and the extent of surgery [7]. The Cancer Children Study Group (CCSG) study has pointed out the dismal prognosis of large infiltrating tumours (T3/T4), and the presence of metastasis [4]. Bloom, in the first study of the International Society of Paediatric Oncology (SIOP),

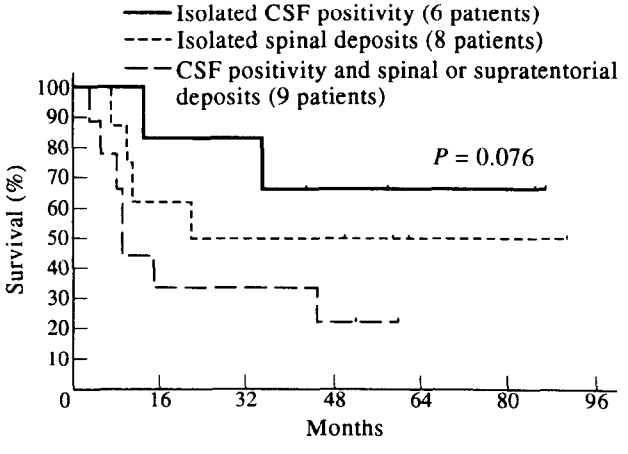


**Figure 2. Event-free survival as a function of metastatic disease.**

defined three unfavourable prognostic factors, namely brainstem infiltration, incomplete removal and presence of metastasis [8]. In recent reports, such prognostic factors have been re-assessed. The SIOP II study does not confirm the results of the SIOP I, since high-risk patients in the SIOP II trial have an identical and sometimes better outcome than low-risk patients [9]. However, in most of the studies, metastatic patients have not yet been assessed separately. One of the goals of the M7 study was to classify the patients according to the results of a strict initial staging, including postoperative CT scanning or MRI compared with the operative notes, CSF examination performed more than 10 days postsurgery and myelogram. Only 2 patients had an MRI study of the neuraxis instead of the myelogram. A second objective was that consecutive patients received the same treatment, according to the results of the initial staging. The treatment of patients with metastatic disease differed from that of low-risk patients only in that they received radiotherapic boosts to macroscopic deposits, and four additional courses of chemotherapy after completion of radiotherapy.

One of the most important aspects of any staging system is the evaluation of the incidence of metastatic disease. Our incidence (23/68: 34%) is similar to that reported in the literature. However, since most reported studies of medulloblastoma have not considered full initial staging as a prerequisite, many patients are classified as Mx or as M0, without any initial data on either CSF examination or myelogram [4, 10, 11). Precise definition of secondary localisations has specific implications for the management of patients. One question in medulloblastoma is to know whether the tumour size (T) is more appropriate than the metastases (M) to define high-risk patients. The TM classification for medulloblastoma was proposed by Chang in 1969, based on a retrospective analysis of the operative notes of 100 patients [7]. Only 3 patients in Chang's report were considered as M2, 11 as M3 and no patient had CSF examination. Due to the low incidence of metastatic patients in this series, Chang analysed the outcome according to the T classification. The major development of modern imaging has considerably changed the patterns of this disease. With the CT scan and the myelogram, the respective proportion of M1, M2 and M3 patients is 13, 5 and 26% in Deutsch's report [12], and 9, 3 and 22% in our series of 68 patients. The use of MRI with contrast material might detect even more metastases.

The overall 7-year survival of metastatic patients is 43% in our study. This is in marked contrast to patients who presented without clinically detectable metastatic disease (Figure 3).

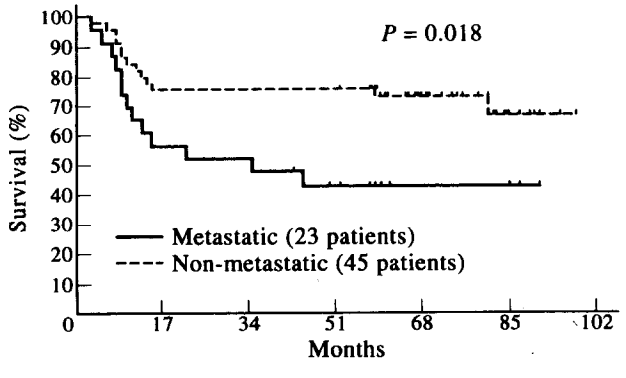


**Figure 3. Event-free survival for patients who presented with metastatic disease compared with patients without detectable metastatis treated with the M7 protocol.**

The first subgroup of patients to consider are those with only isolated CSF positivity. There is no consensus on the implications of CSF involvement. Deutsch has demonstrated that CSF study and myelogram are complementary investigations, and metastatic disease may be detected either as CSF seeding and/or tumour deposits [13]. The prognostic impact of these different findings is a matter of debate. Our study suggests that patients with only CSF involvement have a prognosis similar to those with non-metastatic disease. In our study, the delay between surgery and CSF examination is relatively consistent, and is similar for both localised and metastatic patients. During the postoperative period, can circulating medulloblasts be secondary to the surgical procedure? Should patients with isolated CSF positivity receive more aggressive treatment, since their prognosis seems to be comparable with that of non-metastatic patients? Only one of the two relapses in this group arose in the CSF or the spinal level. In some "localised" cases, complementary information either from biological markers in the CSF (e.g. NCAM, polyamines) or from more accurate imaging studies might alter stage.

Another group was identified, comprising patients with macroscopic spinal deposits. Four had isolated and four had multiple deposits. However, for 1 patient, information on CSF positivity was not available. One patient had clinical signs of spinal compression that required emergency radiation therapy (day 10). The symptoms resolved, and the patient is alive without sequelae. For the other patients in this group, additional radiotherapy was delivered with a local boost of 9–10 Gy to the lesion detected by the myelogram. 4 patients relapsed, 3 of them with supratentorial localisation, isolated (2 cases) or associated with other localisations in the posterior fossa and spinal axis (1 case). However, this group received less supratentorial radiation than the other groups (Table 1), and this may explain the increased supratentorial relapse rate. Though there are few patients, there seems to be no difference between single and multiple spinal deposits.

The last subgroup comprised 9 patients with combined CSF and SD metastases. This combination is probably important since the outcome was worse. One patient died of toxicity during aplasia. Six relapses occurred, three were isolated to the posterior fossa and three associated two or more sites of relapse.

The optimal radiation dose to the posterior fossa has been well defined in medulloblastoma [14]. However, little is known about the optimal radiation dose to the craniospinal axis. The goal of treating the whole craniospinal axis is to eradicate clonogenic tumour cells within the CSF thereby preventing subarachnoid metastases, and in metastatic patients to achieve local control of secondary lesions. However, a substantial proportion of treatment-induced morbidity is related to irradiation of areas distant from the primary site [3]. Recent trials have failed to demonstrate the efficacy of doses as low as 25 Gy to such distant sites. The recommended dose remains 35 Gy [9, 15]. Our study suggests that 30 Gy might be an appropriate dose for high-risk patients, since 75% of the patients who received 30 Gy or more on the whole brain are currently alive and disease-free. Moreover, a review of the radiotherapeutic treatment among the relapsing patients of this series has indicated the impact of quality control in such a multicentric study [5].

The SIOP I [8] and the CCSG 942 [4] studies proposed a regimen, including weekly injection of vincristine, during radiotherapy followed by eight courses of vincristine and CCNU cycled every 6 weeks (plus prednisone in the CCSG study). One criticism was the choice of a chemotherapeutic regimen without

well-proven efficacy in medulloblastoma [16]. The 8 in 1 regimen and high-dose methotrexate have demonstrated an excellent activity in phase II studies [17–19]. Unfortunately, in our experience, the use of intensive chemotherapy with this protocol did not compensate for any reduction in radiation dose, since the majority of patients with a reduced dose (less than 30 Gy) relapsed.

Radiation dose reduction remains an important challenge in order to prevent late neuropsychological and endocrine sequelae, and attempts should be made to evaluate new treatment strategies, such as pre-operative chemotherapy [20], massive chemotherapy with bone marrow transplantation [21] or targeted therapy with radiolabelled antibodies [22]. However, while we wait for more accurate and reproducible means to define poor-risk and high-risk patients, metastatic patients should be considered as the population requiring more aggressive treatment modalities.


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