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Ploidy and Proliferative Index in Medulloblastoma: Useful Prognostic Factors?

Diana M. Tait, Rosalind A. Eeles, Richard Carter, Susan Ashley and Michael G. Ormerod

Paraffin sections from 32 patients with primary medulloblastoma were analysed by flow cytometry for DNA ploidy and proliferative index to assess the value of these measurements in determining prognosis. Twenty-seven samples were informative. Of these 27 patients, 8 had had a total resection. The tumours were diploid in 13 patients and aneuploid in 14. Neither ploidy nor S-phase fraction were prognostic factors for survival, even when considered in conjunction with the type of surgery performed. This is in contrast to other published data, emphasising the need for large multicentre studies of biological prognostic factors in this rare tumour.
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INTRODUCTION

ALTHOUGH SINGLE centre studies report 5-year survival rates in the order of 70–80%, multicentre trials suggest that the overall survival for medulloblastoma is less satisfactory and more in the region of 50–55% [1–3]. In addition, the late toxicity associated with conventional treatment of surgery plus postoperative cranio-spinal irradiation, with a radiation boost to the posterior fossa, is not insignificant and may have important consequences on the quality of life of survivors.

The aim of future therapeutic manoeuvres is 2-fold; to improve survival and, at the same time, decrease the toxic effects of treatment. This can only be achieved if reliable prognostic

Table 1. Patient, tumour and treatment characteristics

Patient no.	Sex	Age at diagnosis*	Extent of surgery	Chemotherapy	Dead/alive	Survival (months)	Ploidy	S-phase fraction
1	F	8	Subtotal	Yes	Dead	11	Aneuploid	High
2	M	12	Total	Yes	Dead	65	Aneuploid	High
3	M	11	Subtotal	No	Dead	30	Aneuploid	High
4	F	9	Total	Yes	Alive	3	Aneuploid	High
5	M	9	Total	Yes	Dead	8	Aneuploid	High
6	F	13	Total	Yes	Dead	47	Aneuploid	High
7	M	9	Subtotal	Yes	Alive	43	Aneuploid	High
8	M	5	Subtotal	Yes	Alive	139	Aneuploid	Low
9	M	5	Subtotal	Yes	Alive	127	Aneuploid	Low
10	M	6	Subtotal	Yes	Alive	84	Aneuploid	Low
11	M	15	Subtotal	Yes	Dead	7	Aneuploid	Low
12	M	8	Total	Yes	Dead	8	Aneuploid	Low
13	M	3	??	Yes	Alive	34	Aneuploid	Low
14	M	15	Total	No	Dead	4	Aneuploid	Low
15	F	14	Total	Yes	Dead	85	Diploid	Equivocal
16	M	9	Subtotal	Yes	Alive	107	Diploid	High
17	M	9	Subtotal	No	Dead	33	Diploid	High
18	M	12	??	Yes	Dead	20	Diploid	High
19	M	8	Subtotal	Yes	Alive	125	Diploid	High
20	M	5	Subtotal	Yes	Dead	8	Diploid	High
21	F	9	Subtotal	Yes	Alive	57	Diploid	High
22	M	1	Total	Yes	Dead	7	Diploid	High
23	F	6	Subtotal	No	Dead	2	Diploid	Low
24	F	6	Subtotal	Yes	Alive	78	Diploid	Low
25	F	1	Subtotal	Yes	Alive	74	Diploid	Low
26	F	7	Subtotal	Yes	Dead	16	Diploid	Low
27	M	3	Subtotal	Yes	Alive	58	Diploid	Low

* Range = 1–15 years; median = 8 years.

factors allow children to be assigned to treatments of varying intensity appropriate to the predicted natural and treatment-related history of their individual disease. Clinical prognostic factors have been defined in a number of studies but are not entirely consistent. For example, in some studies the extent of surgery seems to be an important discriminator whereas in others it has no bearing on outcome [3–6]. The confusion of the situation is demonstrated by the discordance between the first and second SIOP studies in medulloblastoma. From the findings of the first study, prognostic factors were defined such as extent of surgery, brain-stem involvement and Chang T stage [2]. These factors were subsequently used to stratify patients according to risk in SIOP II but recent analysis of this second trial challenges the validity of these factors with the "high" risk patients having the same survival as the "low" risk group [3].

The lack of reliable clinical factors urges the establishment of valid biological indicators of outcome. Ploidy and S-phase fraction provide a measure of tumour grade and cell proliferation and have been widely applied to malignancies in adults [7]. To see whether they might be of value in medulloblastoma, ploidy and S-phase were investigated in a series of patients referred to the Royal Marsden Hospital between 1974 and 1987.

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PATIENTS AND METHODS

Patient population

Between 1974 and 1987, 69 children (< 16 years) with newly diagnosed medulloblastoma were referred to the Royal Marsden Hospital for postoperative treatment, surgery having been performed at a number of centres both within the U.K. and overseas. Paraffin sections were requested from the referring centre of the children operated on in the U.K. and 32 were made available for study. These were subjected to flow cytometric analysis to determine DNA ploidy and S-phase fraction. The histology was reviewed, and confirmed medulloblastoma in all instances. Hospital case notes were reviewed to collect patient details and survival curves were plotted using the Kaplan–Meier method [8]. Univariate analyses were performed to assess the effects of extent of surgical resection, age at diagnosis, tumour ploidy and S-phase fraction on survival.

Patient, tumour and treatment characteristics for the group studied are listed in Table 1. All patients received standard postoperative radiotherapy consisting of whole cranio-spinal axis irradiation with a boost to the posterior fossa. Whole brain doses ranged from 30 to 43 Gy, posterior fossa doses from 50 to 55.5 Gy and spinal doses from 26 to 35 Gy. All but 4 patients received chemotherapy, the scheduling, drug combination and dosage of which varied over the time period under consideration. The overall survival at 5 years was 55%, and all deaths except one were from recurrent medulloblastoma within the central nervous system.

Preparation of the tumour samples for flow cytometry

Three 30 μm thick sections were cut from each tumour block and the nuclei extracted according to the method described by

Hedley *et al.* [9]. The nuclei were stained with propidium iodide at a concentration of 10 μg/ml.

Flow cytometry

Analysis was performed on an Ortho Cytofluorograf 50H equipped with a Lexel 50 mw argon-ion laser tuned to 488 nm and an Ortho 2150 computer system. The parameters measured were forward and orthogonally scattered light and red (propidium iodide-DNA) fluorescence (> 630 nm). Between 10^4 and 2×10^4 nuclei were analysed. A two parameter plot (cytogram) of the peak from the signal from DNA fluorescence versus its integrated area was displayed and a region set to exclude clumped nuclei and debris from further analysis. A cytogram of 90° versus forward angle light scatter was then displayed and a region set to exclude, as far as possible, material from degraded nuclei which scatter less light. The quality of DNA histograms obtained was quantified by measuring the coefficient of variation across the G1/G0 peak. This is defined as: (100 S.D.)/(peak channel). The coefficients of variation of the samples in this study varied from 6 to 11% with a mean of 9%. If the coefficient of variation was greater than 11%, then the sample was excluded from the study (2 patients). In 3 patients there was insufficient material for analysis. The DNA index (DI) was calculated as the ratio of the DNA content of the tumour cells to the content of the diploid normal cells in the sample. A sample was classified as aneuploid if the G1/G0 peaks from the tumour cells could be resolved from those from the normal diploid cells (Fig. 1). The resolution depended on the coefficient of variation of the G1/G0 peak. Generally, an aneuploid tumour with a DNA index less than about 1.15 would not have been resolved and would have been classified as diploid.

An estimate of the percentage of cells in S, G2 and M phases of the cell cycle was taken to be a measure of proliferative activity. The estimate was made by setting a region on the DNA histogram to exclude the G1 peak, and to include the part of the S phase clear of G1 together with G2/M. In the case of diploid tumours, the S + G2/M fraction will therefore have been underestimated as the G1/G0 peak will have been contaminated with normal cell nuclei. The mean value of S +G2/M was calculated separately for aneuploid and diploid tumours. Those samples whose values fell above the mean were scored as "high S", and those below the mean as "low S". For aneuploid tumours, the mean proliferative fraction was 29% and the range was 5–64%. For diploid tumours, the mean was 19% and the range 8–36%.

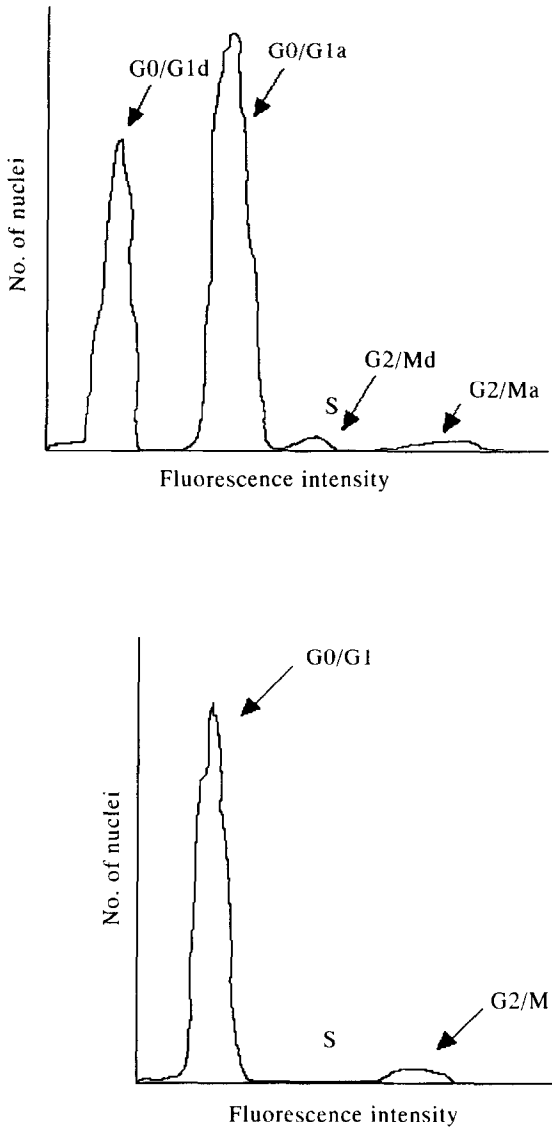

Fig. 1. The upper diagram is a DNA histogram of diploid (d) and aneuploid (a) cells and the lower diagram is that of a pure diploid cell population. The labels refer to the phases of the cell cycle.

RESULTS

The disease-free survival for the entire group of patients referred between 1974 and 1987 is shown in Fig. 2 together with the disease-free survival for the 27 patients in whom paraffin embedded material was available for study. There is no significant difference between the two curves indicating that, despite necessary selection, the patients studied were representative of the group as a whole.

Prognostic factors

Of the factors investigated for prognostic value only extent of surgery correlated significantly with survival. However, unexpectedly, patients undergoing subtotal resection seemed to have a better survival than those in whom the tumour was totally resected ($P < 0.025$). This may be because total resection is so difficult to define, particularly retrospectively. There was no correlation between patient age, sex or radiation dose to the posterior fossa and patient outcome.

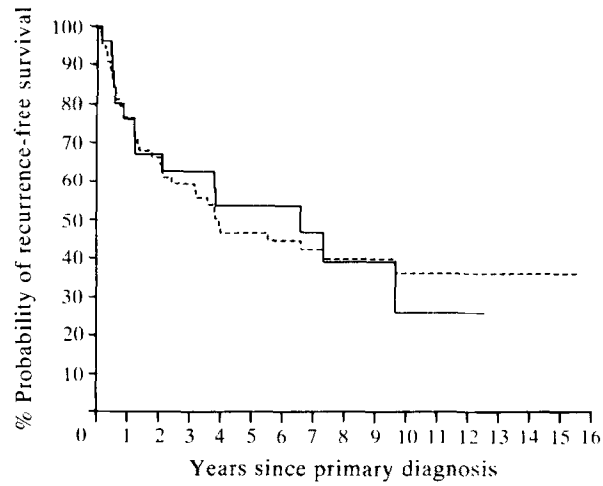

Fig. 2. Disease-free survival of all patients with medulloblastoma 1974–1987 (---) and patients analysed in our study (——).

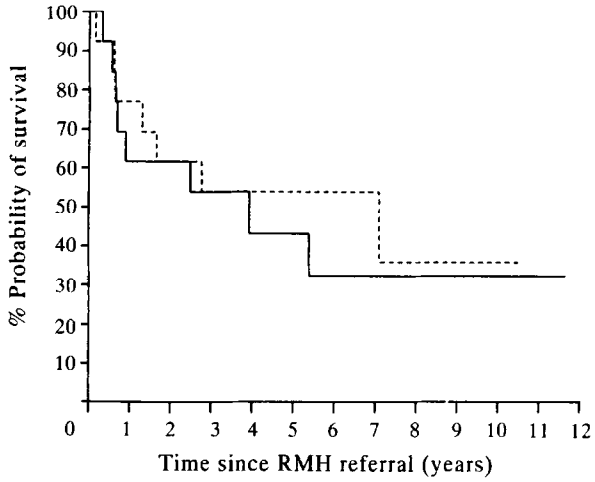

Fig. 3. Overall survival by ploidy status. Aneuploid (——) and diploid (---).

Thirteen tumours were classified as diploid, and 14 as aneuploid. Overall survival as ploidy status is shown in Fig. 3. There was no difference in survival between diploid and aneuploid tumours. There was also no statistically significant difference in survival between tumours with a high and low percentage S-phase (data not shown). Because of a previous report in the literature [10], totally resected aneuploid tumours were compared with subtotally resected diploid tumours but again there was no significant difference in survival but numbers are small (Fig. 4).

DISCUSSION

The results presented failed to show any prognostic value for ploidy or S-phase fraction in this group of patients with medulloblastoma. In a previously reported series, of a similar size and from a single institution, ploidy was reported to correlate with outcome although, similar to the present results, S-phase fraction has no prognostic value [10]. In the previous study [10], further analysis showed an improved outcome for patients with aneuploid tumours who had undergone total resection compared with those patients who had subtotal resection of diploid tumours. In studies of this sort, subgroup analysis is very likely to provide positive results and the absence of an association in the present study supports the possibility that this result arose by chance alone. Other reports of flow cytometry in medulloblastoma have involved only very small numbers of patients [11–14].

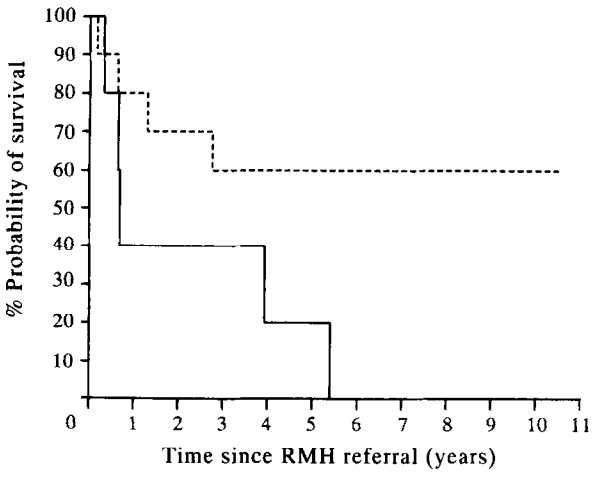

Fig. 4. Overall survival by surgery and ploidy status. Total resection aneuploid (——) subtotal resection diploid (---) $P > 0.1$.

Nuclei extracted from paraffin blocks can give DNA histograms of surprisingly good quality (as measured by the coefficient of variation of the peaks in the histogram and the lack of degraded material). In our experience, this quality is determined by the manner in which the tissue is handled before and during fixation. In this study, because of the rarity of the tumour, the blocks came from different centres and were up to 15 years old. We had no control over the handling of the tissue and the quality of the histograms obtained was lower than those obtained from other tumours handled within the Royal Marsden Hospital during the last 10 years. For this reason, we used a crude measure of cells in S+ G2/M phases as a measure of S phase fraction and hence proliferation.

From the available data on ploidy in other childhood tumours there appears to be a polarisation of effect. For example, for acute lymphoblastic leukaemia and embryonal sarcomas, hyperploidy is associated with a favourable outcome [15, 16]. Conversely, in Wilms' tumour, osteosarcoma and alveolar rhabdomyosarcoma hyperploidy seems to confer a poor prognosis [17–18]. In neuroblastoma the influence of ploidy seems to be complicated by age with hyperdiploidy being a favourable factor in young but not in older children [19]. The collection of extensive data on ploidy in neuroblastoma has only been possible by the incorporation of biological studies into multicentre trials.

For the other paediatric malignancies, studies of biological markers have generally been performed in single institutions on small patient numbers. In order to accurately determine their value and avoid conflicting and confusing results between small series, these parameters must be incorporated into future multicentre trials in which large numbers of patients are treated in a standard fashion. The new UKCCSG/SIOP PNET Study III has made provision for this and should provide an assessment of these biological factors in a childhood malignancy which sorely needs reliable prognostic indicators.

In such a multicentre study, a choice must be made between recording a DNA histogram from fixed or unfixed (fresh or frozen) material and between using one or several flow cytometry laboratories. In our experience, the quality of DNA histograms from tissue fixed in buffered formal saline and embedded within 24 h of fixation can be as good as those from fresh tissue. Collection and storage of unfixed tissue can cause problems, particularly with a rare tumour. We would, therefore, recommend that material is used from paraffin blocks. This has the additional advantage that blocks can be sent to one laboratory for analysis avoiding any inter-laboratory variation.

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Fractionated Stereotactic External Beam Radiotherapy in the Management of Brain Metastases

R.W. Laing, A.P. Warrington, F. Hines, J.D. Graham and M. Brada

24 patients with 28 brain metastases were treated with fractionated stereotactic radiotherapy (SRT). Doses ranged from 10 Gy in two fractions to 20 Gy in two fractions. 13 patients received SRT boost after whole brain radiotherapy (WBRT), 5 were treated with SRT alone and 6 were treated at the time of recurrence following WBRT. The median progression-free survival at the treated site was 18 months and the median survival was 18 months. All patients were treated without admission to hospital. Toxicity of fractionated SRT was minimal and patients treated without WBRT did not suffer significant alopecia. Fractionated SRT offers a non-toxic non-invasive alternative to excision surgery in patients with solitary brain metastases. The optimum fractionation schedule and the role of whole brain irradiation remain to be determined.
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INTRODUCTION

ALTHOUGH WHOLE brain radiotherapy (WBRT) achieves useful palliation of symptoms in 60–80% of patients with brain metastases, approximately 50% of patients die with uncontrolled brain disease [1]. Increasing radiation dose to the whole brain in the presence of multiple lesions [1] or wide field boost to a limited volume of the brain [2] does not improve symptomatic control or survival.

Approximately 40% of patients have solitary brain metastases [3] and radical treatment with excision in addition to WBRT improves local control and survival [4]. Focal irradiation either in the form of brachytherapy or stereotactic external beam radiotherapy (SRT)/radiosurgery can be considered as an alternative to surgical excision. It has been employed to gain local control of small intracranial tumours such as acoustic neuroma [5], or recurrent gliomas [6]. In the treatment of solitary metastases SRT has been used largely as single fraction treatment

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